

Revised Twelfth Edition

PHARMACOLOGY AND PHARMACOTHERAPEUTICS

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**R. S. SATOSKAR
S. D. BHANDARKAR**

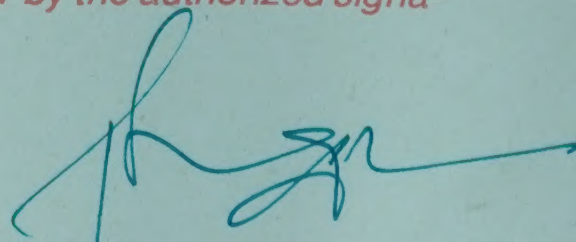


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PHARMACOLOGY
AND
PHARMACOTHERAPEUTICS

Satoskar, Kale, Bhandarkar's

PHARMACOLOGY AND PHARMACOTHERAPEUTICS

TWELFTH EDITION

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Preface to the Twelfth Edition

This twelfth edition has been extensively revised to bring it up to date with the current concepts in Pharmacology and Pharmacotherapeutics. Several new drugs are described and new section added. Many sections have been rewritten. This has been balanced by deleting obsolete drugs and sections. The chapter on "Radioactive Isotopes and Biological Effects of Radiation" has been dropped from this edition as several texts dealing with the subject are available. Readers are referred to the previous editions of this book for information on that subject.

We are grateful to our colleagues for their valuable comments and constructive criti-

cism while preparing this edition. We extend our special thanks to : Dr. B. S. Kulkarni, Emeritus Prof. of Biochemistry, Seth G. S. Medical College, Bombay, for his help in revising appendix B and to Dr. S. D. Sule for preparing the index. We thank the authors and the publishers who have graciously allowed us to reproduce certain tables and diagrams in this edition.

We will continue to welcome suggestions and comments on the material presented in this edition.

Bombay
January, 1991

R. S. Satoskar
S.D. Bhandarkar

Dosage Note

Special care has been taken by the authors and the publishers of this book to ensure that dosage recommendations are precise and in agreement with standards officially accepted at the time of publication. However, it may be noted that such drug schedules are often changed in the light of accumulating clinical experience and continuing laboratory studies. This is more true in the case of products introduced recently. We, therefore, urge the readers to refer to the manufacturers' recommendations for dosage, especially for the new drugs and for those used infrequently in clinical practice.

Preface to the First Edition

Pharmacology has undergone a phenomenal growth during the last twenty years and drug therapy now forms a major aspect of therapeutics. So far, pharmacology was traditionally associated with the study of drugs in dogs, cats and rats, while therapeutics or clinical application was regarded as an entirely independent and a mystical skill. Now it is generally agreed that the major object of teaching pharmacology to the medical students is to provide a rational basis for choosing and using drugs skilfully to relieve patients' ailments. This is becoming more and more important as the practising doctor is now confronted with so called "newer drugs" at such a great pace that even a full-time pharmacologist sometimes finds it difficult to keep abreast of their merits and demerits. It is highly desirable, therefore, that students of pharmacology should be educated to develop a critical outlook towards various drugs, as they are introduced. This means that the book on pharmacology meant for medical students should not only give detailed account of various pharmacological actions but should also furnish a critical appraisal of their present day use in therapeutics. We have attempted in this book to combine these two important aspects. In addition, an outline of experimental evaluation of drugs in animals and man is also provided. While doing this, it was thought essential to give the relevant information from other disciplines like physiology, pathology and clinical medicine. This, though a repetition to a certain extent, is no doubt useful to understand the basis of rational therapeutics. After all, pharmacology is in some respects a bridge between basic

medical sciences on one hand and clinical medicine on the other. Most of the presently available text books, except a few classics written by many authors, fail to achieve this goal. It is a common experience of those who teach pharmacology in this country to find it difficult to recommend one single book to the undergraduate medical students. Many books which give excellent information about pharmacological actions treat the therapeutics very cursorily while others that give delightful therapeutics probably assume that students know most of the basic pharmacology. It is not practicable to recommend routinely the classical multi-author books to undergraduate students, as they have many other subjects to go through, which are equally important and advanced. This book is written to fill up this gap between a big book and a concise, less informative work, so that students will get all the necessary information by reading one book. While doing this, obviously we have to restrict the size of the book, lest it would be unwieldy and defeat the very purpose for which it is written. In order to achieve this, history and chemistry are reduced considerably while diagrams are included strictly to facilitate the understanding of the subject. The coverage is given according to the importance of the subject in therapeutics. Wherever multiple drugs of similar type are available, only the important prototype is discussed in detail, while others have received only a brief mention.

Although the book is written mainly for undergraduate medical students, it will also prove useful to post-graduates and practising doctors. The therapeutics part includes many

details so that the book would continue to be useful even after passing pharmacology and is expected to serve as a pharmacotherapeutic reference work. The big multi-author books on this subject are no doubt excellent and authoritative but are not easily accessible to practising doctors at the time of emergency. In such circumstances this book should find its use.

The book is not written 'with an eye on examination' but it is the hope of the authors that by reading this book students would develop an attitude of thinking towards newer drugs which are many times made to appear like "therapeutic marvels". It is not expected that undergraduate students should 'cram' this book and try to remember everything that is given. It is neither possible nor necessary. They are expected to learn the basic pharmacology of the drugs in common clinical use and their rational application in therapeutics. However, the authors will feel rewarded, if students can grasp the ideology and spirit behind presentation of this book.

Drug therapy related to tropical problems is emphasized; this topic is often dismissed summarily in other works of this size. Proprietary names are included wherever necessary so that their pharmacological identity is recognised by the reader. No detailed reference list is given as this would have added many more pages. Instead, the books, reviews, symposia and monographs referred to are enlisted at the end of the book. The enthusiastic reader may refer to

these for a more extensive reference list. Preparations included in the Indian Pharmacopoeia are marked as I.P. and those included in British Pharmacopoeia are listed in a separate list at the end.

It is not possible to present a book of such a size without generous help of others and the authors are deeply grateful to their many colleagues at Seth G. S. Medical College and Lokmanya Tilak Municipal Medical College, Bombay. Particularly, the help rendered by Drs. B. S. Kulkarni, S. M. Chittal, S. V. Gokhale, M. G. Wagh, C. H. Kewalramani, Mr. N. K. Dadkar, Mr. V. S. Jathar, Dr. S. M. Karandikar and Miss P. Mirwankar is gratefully acknowledged. We also would like to express our grateful thanks to many authors and publishers who promptly conceded our requests and granted permission to reproduce certain tables and diagrams, as indicated in the text. We are greatly indebted to Dr. A. F. Golwalla, Hon. Professor of Medicine, Seth G. S. Medical College and K.E.M. Hospital, Bombay for his encouragement and permission to reproduce E.C.G. records. Finally, our thanks are due to Popular Prakashan and Popular Press (Bom.) Pvt. Ltd., who as publishers and printers respectively are responsible for delivering this book in your hand expeditiously.

Bombay,
November, 1968

R. S. Satoskar
A. K. Kale
S. D. Bhandarkar

Section I : General Considerations

1 General Pharmacology

The subject of 'Drugs' is as old as disease. Illness has been man's heritage from the beginning of his existence and the search for remedies to combat it is perhaps equally old. The world's oldest pharmacological or therapeutic writings come from India and China. The great herbal or Chinese materia medica 'Pan Tsao' was probably written in 2735 B.C. and contained many vegetable and metallic preparations and a few animal products including toad's eyelids, elephant's and tiger's bones, horns, fins and such material. The earliest Indian records are the *vedas*. Although there are medical descriptions in *Rigveda* (2500-3000 B.C.), it was *Charaka*, a renowned ancient Indian Physician, and later *Sushruta* and *Vagbhata*, who described various medicinal preparations included in Ayurveda, the science of life. Initially, these consisted mostly of non-poisonous vegetable drugs and minerals. Thus, *Charaka* described about 300 vegetable drugs and classified them according to their effects, mostly on symptoms, into 50 groups. The original Ayurvedic materia medica was later superseded to some extent by the alchemic or chemical substances at about the beginning of Christian era. The earliest sources of Western medicine come from Egypt and the two kingdoms of Assyria and Babylonia. The 'Papyri' were the first written account of medical experiences from Egypt, and date back to 1900 B.C. The papyrus discovered by Eber in 1872 was prepared in 1500 B.C. and mentions about 700 herbal remedies, including opium. A Babylonian clay tablet (700 B.C.) has been discovered which mentions about 300 drugs. Modern medicine is considered to date from Hippocrates, a Greek physician (450

B.C.), who for the first time introduced the concept of disease as a pathologic process and tried to organize the science of medicine on the basis of observation, analysis and deduction. Hippocratic practice did not include extensive use of drugs, probably because he did not believe in shotgun or magical remedies, but instead recommended judicious use of simple and efficacious drugs.

Till the beginning of the 19th century, the treatment of diseases consisted of such obnoxious remedies as flesh, excreta and blood of various animals along with a few metallic and plant preparations. James Gregory (1753-1821) was responsible for popularizing heroic symptomatic treatment consisting of blood letting, large doses of emetics and drastic purgatives, often with disastrous results. Such treatment without any rational basis was called 'Allopathy' (meaning the other suffering), a term which is still wrongly applied to denote the system of modern scientific medicine, as opposed to Homeopathy.

The concept of Homeopathy was first introduced in the early 19th century by Hannemann who thought that like cures like, and that dilution potentiates the action of drugs. Homeopathy outlines the therapy for various ailments with drugs in very high dilutions. The claims are, however, difficult to understand in the light of present concept of diseases nor can they be substantiated by various experimental methods applied to the study of modern medicine.

Development of modern pharmacology as a science is fairly recent and probably started taking shape following the introduction of experimental procedures in animals by Francois

Magendie (1783-1855) and Claude Bernard (1813-1878). Till then, the treatment of diseases was empirical, based on combination of guess work and experience. Spectacular developments in physiology, biochemistry and organic chemistry have greatly accelerated the advances in pharmacology. In its turn, pharmacology has helped to elucidate many basic physiological and pathological mechanisms in health and disease.

Various animal experiments have been designed to study the effects of drugs on living organisms and isolated tissues, and these give an insight into where and how a drug acts. The emphasis on critical scientific inquiry has enabled modern scientific medicine to incorporate useful remedies from other, older disciplines including the Ayurveda. For the rational treatment of diseases, knowledge of the mode of action of a drug, its effects on various body systems and the probable adverse effects is important. The object of pharmacology, which is in fact a branch of biology, therefore, is mainly to provide such scientific data in both animals and humans, and this forms the basis of rational therapeutics.

Pharmacology is the science that deals with drugs. The word is derived from Greek words *Pharmacon* (an active principle) and *logos* (a discourse or treatise).

The word 'drug' is derived from the French word *drogue*, a dry herb. A drug is defined as any substance used for the purpose of diagnosis, prevention, relief or cure of a disease in man or animals. According to W.H.O. "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient".

Pharmacology consists of detailed study of drugs, particularly their actions on living animals, organs or tissues. The actions may be beneficial or harmful. It includes such allied fields as :

(1) **Pharmacognosy** which is the science of identification of drugs.

(2) **Pharmacy** which is the science of identification, selection, preservation, standardisation,

compounding and dispensing of medicinal substances.

(3) **Pharmacodynamics** which is the quantitative study of the biological and therapeutic effects of drugs (what the drug does to the body). Such studies also elucidate the mechanism of action of a drug and may correlate the drug actions with their chemical structure. The term **Pharmacokinetics** is used to describe the study of the absorption, distribution, metabolism and excretion of drugs and their relationship to pharmacologic response (what the body does to the drug).

(4) **Therapeutics** which means to care for, to tend to or to nurse, is a branch of medicine concerned with the cure of disease or relief of symptoms and includes drug treatments.

(5) **Toxicology** which is the science of poisons. Poisons are substances that cause harmful, dangerous or fatal symptoms in animals and human beings; many drugs in larger doses act as poisons. Measurement and detection of poisons as well as treatment of poisoning are included in this science.

(6) **Chemotherapy** which is concerned with the effect of drugs upon micro organisms and parasites, living and multiplying in a living organism. It now includes the drug treatment of cancer.

Materia medica is the older term for a branch of pharmacology concerned with sources, description and preparation of drugs.

Pharmacopoeia is an official code containing a selected list of the established drugs and medicinal preparations with descriptions of their physical properties and tests for their identity, purity and potency. Pharmacopoeia defines the standards which these preparations must meet and their average doses for an adult. A few well-known pharmacopoeias are the Indian Pharmacopoeia (I.P.), the British Pharmacopoeia (B.P.), the United States Pharmacopoeia (U.S.P.) and the European Pharmacopoeia.

National Formulary is published by the American Pharmaceutical Association. **British National Formulary** (B.N.F.) is published by the British Medical Association and the Pharma-

ceutical Society of Great Britain. They include formulae for pharmaceutical preparations such as elixirs, solutions, tinctures and powders 'whose use or effectiveness is reasonably certain'. National formulary (N.F.) of India is published by the Government of India.

British Pharmaceutical Codex is published by the Pharmaceutical Society of Great Britain. It gives information of drugs, other pharmaceutical substances and formulated products. Further, it provides standards for identification and purity for a range of substances and materials for which standards are not provided by the B.P.

AMA Drug Evaluations: This is a publication of the American Medical Association (AMA) Council on Drugs. Its main goal is to provide physicians and other health care professionals with up-to-date, unbiased information on the clinical use of drugs. It is intended to serve as a reference source for practical, comparative, evaluative information on drug therapy.

THE NATURE AND SOURCES OF DRUGS

The various sources of drugs are :

I. Mineral : e.g. Liquid paraffin, magnesium sulfate, magnesium trisilicate and kaolin.

II. Animal : e.g. Insulin, thyroid extract, heparin, gonadotrophins, and antitoxic sera.

III. Plant : e.g. Morphine, digoxin, quinine, atropine and reserpine.

IV. Synthetic : e.g. Aspirin, sulfonamides, procaine and corticosteroids.

V. Micro-organisms : Bacteria and fungi, isolated from soil, are important sources of anti-bacterial substances (antibiotics) e.g. penicillin and bacitracin.

VI. Drugs produced by genetic engineering (DNA recombinant technology) e.g. human insulin and human growth hormone.

Majority of the drugs currently used in therapeutics are synthetic.

Plant products : The important pharmacologically active principles in plants are :

(a) Alkaloids, (b) Glycosides, (c) Oils : fixed and volatile, (d) Resins, (e) Oleoresins, (f) Gums, (g) Tannins, (h) Antibacterial substances.

(a) **Alkaloids :** Alkaloids are basic substances containing cyclic nitrogen, which are insoluble in water but combine with acids to form well-defined, water soluble salts. Examples of alkaloids are : morphine, atropine and emetine.

(b) **Glycosides :** These are ether-like combinations of sugars with other organic structures. A glycoside does not form salts with acids but when heated with mineral acids it is hydrolysed to a sugar and a non-sugar component called aglycone or genin e. g. digoxin hydrolyses into digitoxose and digoxigenin. A glycoside which yields glucose on acid hydrolysis is called a glucoside e. g. strophanthin.

(c) **Oils :**

(i) **Fixed oils :** Fixed oils are glycerides of oleic, palmitic and stearic acids. These are fats and many have food value. Many fixed oils are edible and are employed for cooking and as solvents, e. g. peanut oil, coconut oil, olive oil. Castor oil has certain pharmacological actions and acts as a purgative.

(ii) **Volatile oils :** Volatile oils are volatilised by heat and possess aromas. They are also called essential or flavouring oils, as aromas of plants and flowers reside in the volatile oils present. Chemically, they are not fats and are without any caloric value. They contain the hydrocarbon terpene or some polymer of it, which serves as a diluent or a solvent for a more active compound e. g. menthol in peppermint oil.

Volatile oils are used as :

(a) **carminatives :** for expulsion of gas from the stomach, e. g. oil of eucalyptus, asafoetida, ginger,

(b) **antiseptics :** in mouth wash, pastes,

(c) **counterirritants** e. g. oil of wintergreen, turpentine oil,

(d) **flavouring agents** e. g. oil of peppermint and as

(e) **pain relieving agents** e.g. oil of clove in toothache.

(iii) **A mineral oil** e. g. liquid paraffin is a hydrocarbon derived from petroleum and is commonly used as a lubricant purgative. It has no food value.

(d) **Resins** : Resins are found in plants. They are formed by oxidation or polymerization of volatile oils and are insoluble in water but soluble in alcohol.

(e) **Oleoresins** : They are mixtures of volatile oils and resins. Male fern extract, used formerly for tape worm infestation, contains an oleoresin.

(f) **Gums** : These are secretory products of plants. They are dispersible in water and form thick, mucilaginous colloids. Gums such as gum acacia and gum tragacanth are pharmacologically inert and are employed in pharmacy as suspending and emulsifying agents. Agar, another gum, is used as a bulk purgative.

(g) **Tannins** : Tannins are non-nitrogenous plant constituents characterized by their astringent action upon mucous membranes; they precipitate proteins from the cells of the mucous membrane and thus exert a protective action. Substances which release tannic acid in the small intestine, e. g. tincture of catechu, were employed in the treatment of diarrhoea.

(h) **Antibacterial substances** : These are substances derived from moulds and fungi e. g. penicillin, streptomycin.

ROUTES OF DRUG ADMINISTRATION

Drugs can be applied locally or can be administered orally and by injection.

Local application of a dusting powder, paste, lotion, drops, ointment or plaster is used for its action at the site of application. Substances may also be administered locally in the following forms : bougie for urethra, pessary for vagina and suppository for the vagina and rectum.

Drugs used in the form of watery solutions for local effects on mucous membranes are sometimes likely to be absorbed and may produce adverse systemic effects. In case of corneal application, the drug may penetrate into the anterior chamber and affect the ciliary muscle e. g. cocaine. Similarly, during irrigation or spraying of the nose, a compound may find its way into the middle ear through the eustachian tube. Instances of lipoid pneumonia following aspiration of an

oily solution into the respiratory tract have been reported.

Enemata : Administration of a medicament in a liquid form into the rectum is called enema. Enemata are of two types :

(i) *Evacuant enema* : e. g. soap water enema. The aim is to remove the faecal matter and the flatus. The water stimulates the rectum by distension while soap acts as a lubricant. The quantity of fluid administered at a time is about 600 ml. The enema is useful in treating selected cases of constipation. It is also administered before surgical operations, delivery and radiological investigation of the gastrointestinal tract.

(ii) *Retention enema* : The fluid containing the drug is retained in the rectum so that the drug may act locally as in prednisolone enema in ulcerative colitis; or may act systemically after absorption through the mucous membrane e. g. paraldehyde enema for production of basal anaesthesia; the latter is not used in clinical practice any more. The quantity of fluid administered in retention enema is usually 100-120 ml.

Oral or Enteral route : This is the most commonly employed route for drug administration. Its advantages are that it is safe, convenient and economical, and the complications of parenteral therapy are avoided. However, it has the following disadvantages :

(a) The onset of drug action is tardy.

(b) Irritant and unpalatable drugs cannot be administered by this route.

(c) The route may not be useful in the presence of vomiting and diarrhoea.

(d) The route cannot be employed in an unconscious or an uncooperative patient.

(e) Drugs likely to be destroyed by digestive juices cannot be administered orally e. g. insulin. Further, although a drug like testosterone is absorbed, much of it is inactivated in the liver and little reaches the systemic circulation.

(f) The absorption of certain drugs is irregular or negligible.

Substances administered as pills or capsules are sometimes made more acceptable by various

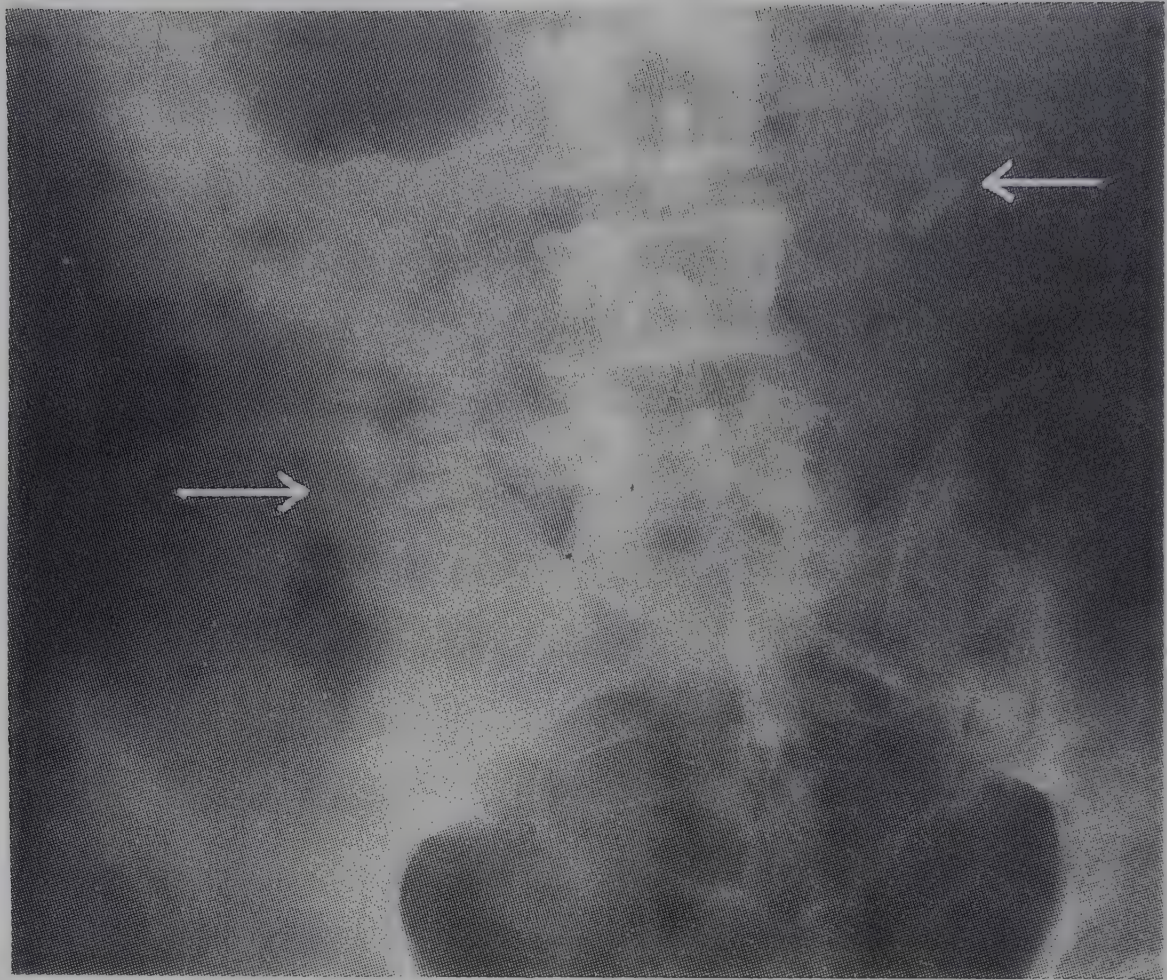


Fig. 1A: Abdominal plain x-ray showing the presence of unabsorbed hard coated tables of a drug in the colon.

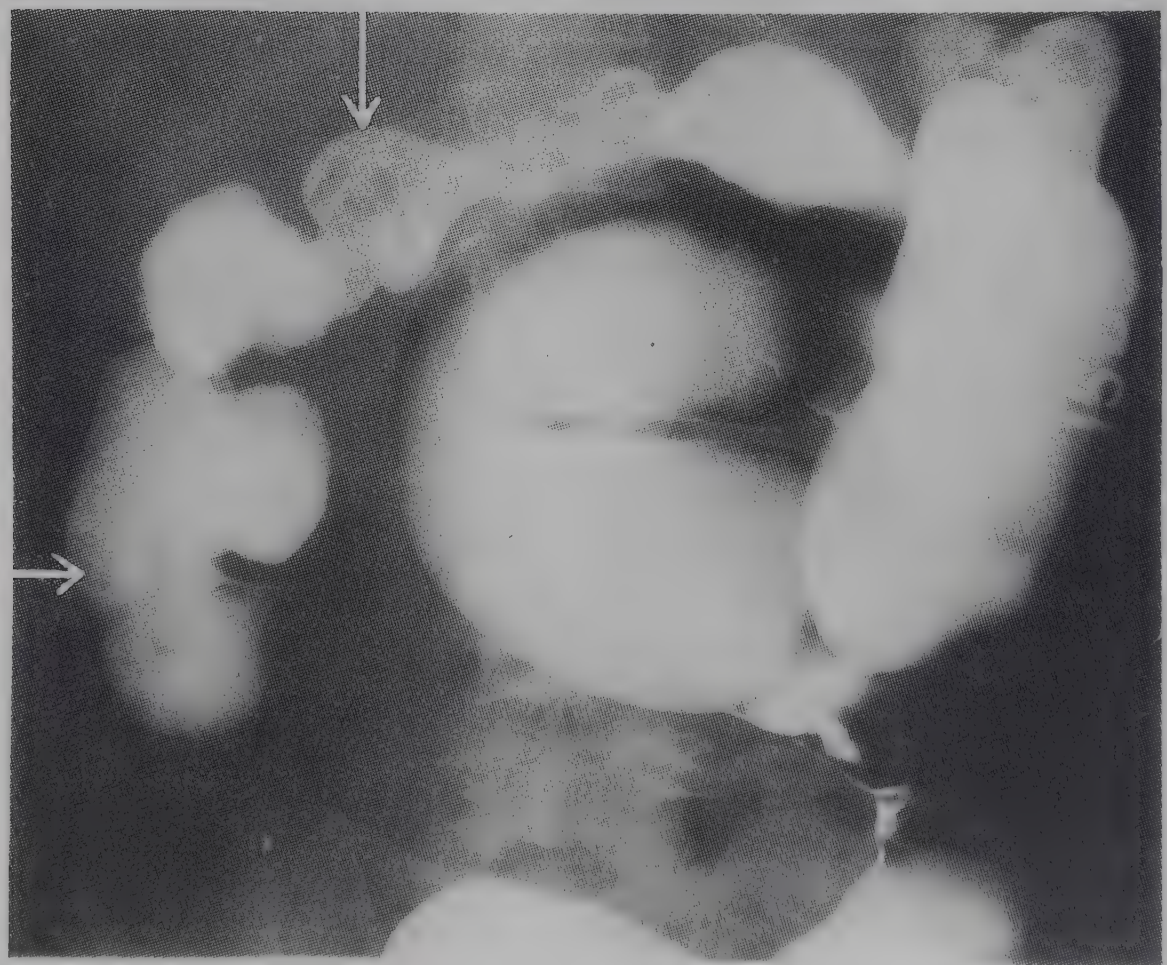


Fig. 1B: Abdominal x-ray barium enema of the same patient.

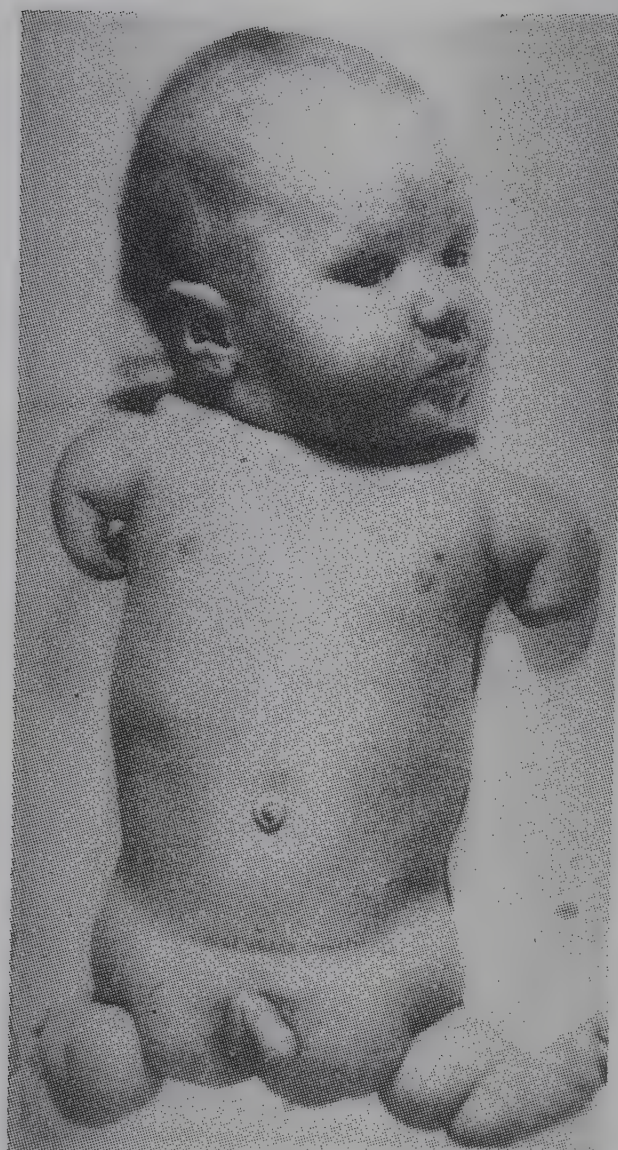


Fig. 1.15: Limb abnormalities (Seal limbs) following thalidomide administration in the mother. (With courtesy of Dr. R. A. Pfeiffer from the Univ - Kinderklinik, Munster. Direktor: Prof. Dr. H. Mai.)
Please see the text, page 35.

coatings such as synthetic resins, gums, sugars, plasticizers, polyhydric alcohols, waxes, colouring agents and flavouring agents.

Certain precautions should be taken during oral administration of drugs. Capsules and tablets should be washed down with a glass of water with the patient in upright posture, either sitting or standing, as this enhances the passage into the stomach and rapid dissolution. Giving drugs orally to a recumbent patient should be avoided, if possible, especially those agents which can damage the esophageal mucosa e.g. tetracyclines, iron salts and slow release potassium preparations.

Enteric coated pills and tablets: Sometimes, pills and tablets are coated with cellulose-acetate-phthalate, gluten and anionic co-polymers of methacrylic acid and its esters. These substances resist the acid juice of the stomach but permit disintegration in the intestinal alkaline juices. Enteric coating is done :

- (i) to prevent gastric irritation and alteration of the drug in the stomach,
- (ii) to get the desired concentration of the drug in the small intestine, and
- (iii) to retard the absorption of the drug.

If the coating is very hard, a tablet or a pill may pass out without being dissolved in the gastrointestinal tract (Fig. 1.A, see art plate), and may fail to produce the therapeutic effect.

The above conventional dosage forms serve only the purpose of introducing specific amounts of drug into the body. They do little to maintain uniform body drug concentration. Further, in order to produce a therapeutic concentration at the site of action one has to administer much larger quantities of the drug which obviously can cause adverse reactions. These dosage forms may have additional disadvantages such as necessity for frequent dosing, problems related to concomitant food intake and patient compliance, particularly during long term therapy. New dosage forms and drug delivery systems are now available to overcome some of the disadvantages. Thus, various *sustained release or time release*

preparations (Timsules, Spansules) for oral use are available, which release the active drug over an extended period of time. Such preparations usually have the particles of drug coated with coatings which dissolve at different time intervals. Thus, the coating which dissolves soon releases an amount of the drug which establishes its action quickly; the other coating dissolves more slowly and ensures a slow release of the remainder of the drug thus providing uniform medication over a prolonged period.

Parenteral route : Routes of administration other than the alimentary tract (the enteron) are called parenteral.

The advantages of the parenteral routes are :

- (a) They can be employed in an unconscious or an uncooperative patient.
- (b) They can be employed in cases of vomiting and diarrhoea and in the patients unable to swallow.
- (c) They avoid drug modification by the alimentary juices and liver enzymes.
- (d) Drugs which might irritate the stomach or which are not absorbed in the small intestine can be administered.
- (e) Rapid action and accuracy of dose are ensured.

Obvious disadvantages are that they are less safe, more expensive and inconvenient for the patient. Further, self medication is difficult, and there is danger of infection if proper care is not exercised. Finally, injury to important structures such as nerves and blood vessel may occur.

The parenteral routes are :

I. Inhalation : Drugs may be administered as solid particles, as nebulized particles from solutions or in the form of vapours. They may be sprayed as fine droplets which get deposited over the mucous membrane producing local effects e. g. salbutamol spray used in bronchial asthma. They can also be administered as gases e. g. volatile general anaesthetics.

Drugs given by this route are quickly absorbed and produce rapid local and systemic effects. Thus, nicotine, morphine and tetrahydrocannabin-

not are rapidly absorbed following the inhalation of tobacco, opium or marihuana smoke.

Blood levels of volatile substances such as anaesthetics can be conveniently controlled as their absorption and excretion through the lungs are governed by the laws of gases.

However, drugs go directly to the left side of the heart through the pulmonary veins and may produce cardiac toxicity. Further, local irritation may result in an increase in the respiratory tract secretions.

II. Injections :

(a) **Intradermal** : This is given into the layers of the skin e. g. B. C. G. vaccine. Only a small quantity can be administered by this route and the injection may be painful.

Intradermal injection is also employed for studying drug allergy.

(b) **Subcutaneous** : Only non-irritant substances can be injected by this route. The commonest drug used by this route is insulin. The drug absorption is slower than with intramuscular and intravenous routes. However, the action is sustained and uniform. Absorption by this route is undependable in shock. Subcutaneous drug implants can act as 'depot' therapy e. g. steroid hormone implants.

In pediatric practice, saline is often injected subcutaneously in large quantities. This procedure is termed *hypodermoclysis*. Drug absorption from the subcutaneous area can be enhanced by the addition of the enzyme hyaluronidase.

(c) **Intramuscular** : In addition to soluble substances, mild irritants, suspensions and colloids can be injected by this route.

The rate of absorption is reasonably uniform and the onset of action is rapid. The volume of injection should not exceed 10 ml. *However, it should be noted that I. M. absorption is not always faster than oral absorption e. g. I. M. diazepam, hydrocortisone, digoxin and phenytoin are absorbed more slowly than the orally given drugs.*

Drugs injected intramuscularly may cause local pain and even an abscess. Care should be taken to see that the injection is not given near a

nerve since an irritant solution can damage the nerve, causing severe pain and even paresis of the muscles supplied by it. Finally, intramuscular injection should not be made into the buttock until the child starts to walk, as the gluteus maximus is very tiny till the child starts to walk; the lateral aspect of the thigh should be used at this age.

(d) **Intravenous** : Drugs given directly into a vein produce rapid action, and the desired blood concentration can be obtained with a well defined dose.

A drug given intravenously may be injected (a) as a bolus e. g. Furosemide; (b) Over 5-10 minutes after it is diluted in 10-20 ml of isotonic glucose or saline e.g. Digoxin or (c) in an infusion which is 50-100 ml. or more in volume. An infusion is employed (i) to slow the administration of the drug e.g. Morphine; (ii) to maintain a constant plasma level of the drug e.g. insulin or dopamine; and (iii) to administer large volumes either rapidly or over prolonged periods of time e.g. fluids in shock or dehydration.

However, once the drug is administered by this route, its action cannot be halted. Further, local irritation can lead to phlebitis. (For prevention of phlebitis, see Chapter 34.) Leakage of the drug outside the vein can produce severe irritation e. g. intravenous iron, nitrogen mustard. Self medication is difficult.

The following precautions should be observed during intravenous therapy :

(i) Before injecting, ensure that the needle is in the vein.

(ii) The injection should be given slowly in case of certain drugs such as iron and aminophylline, as a sudden high blood concentration may be dangerous.

(iii) Only the minimum quantity required to elicit a particular effect should be injected. An additional dose may be administered by the intramuscular route, if necessary.

(e) **Intra-arterial** drug administration produces a sudden high concentration in arterial blood and hence, may be harmful locally or damaging to tissues supplied by the artery. This

route has no advantages except in diagnostic studies, e. g. angiograms, and in the treatment of peripheral vascular disorders. Certain antimalignancy compounds are administered by intra-arterial perfusion in localized malignancies.

(f) **Intrathecal** administration involves introduction of drugs such as spinal anaesthetics into the subarachnoid space. The drugs act directly on the central nervous system. This route also is convenient for producing high local concentrations in the subarachnoid space e.g. certain antibiotics, corticosteroids and antimalignancy drugs. Strict aseptic precautions must be observed.

Lignocaine is now used extradurally to produce anaesthesia for pelvic surgery. The extradural use of morphine for analgesia is described in Chapter 8.

(g) **Intraperitoneal** : This route is useful in infants for giving fluids like glucose saline, as the peritoneum offers a large surface from which they are readily absorbed.

(h) **Intramedullary** : Introduction of a drug into the bone marrow. This route is now rarely used.

(i) **Intra-articular** : Certain drugs are administered directly into a joint for the treatment of local conditions. This ensures a high local concentration of the drug e. g. hydrocortisone acetate in the treatment of rheumatoid arthritis. However, utmost aseptic precautions must be taken during this procedure to avoid the introduction of infection.

III. Transcutaneous :

(a) **Iontophoresis** : In this procedure galvanic current is used for bringing about the penetration of drugs into the deeper tissues where they may act upon the tissues in the neighbourhood of the point of application. Anode iontophoresis is used for compounds bearing positive charges and cathode iontophoresis for the negatively charged compounds. The force of repulsion between similar charges drives the drug ion into the deeper tissues. Salicylates have been used by this method.

(b) **Inunction** : Certain drugs when rubbed into the skin (inunction) can get absorbed and produce their systemic effects e. g. nitroglycerin

ointment in angina pectoris. Certain potent glucocorticoids when applied to skin lesions for local effects may get absorbed and cause systemic adverse effects.

(c) **Jet injection** : This method involves the transcutaneous introduction of a drug by means of a high velocity jet produced through a microfine orifice. This method, which does not require the use of a needle, and is therefore painless, is particularly suitable for mass inoculation programmes. Attempts have been made to develop a jet injector for insulin.

(d) **Adhesive units** : Recently, a transdermal therapeutic system in the form of an adhesive unit has been developed to deliver drugs slowly, producing prolonged systemic effect e. g. scopolamine for prevention of motion sickness.

It must be emphasized that percutaneous absorption of topically applied drugs is significantly greater in infants and children, particularly in prematures and if the skin is burnt or excoriated. This can enhance drug toxicity.

IV. Trans-mucosal route :

(a) **Sublingual administration** : A tablet containing a medicament is placed under the tongue and is allowed to dissolve in the mouth. The active agent thus gets absorbed through the buccal mucous membrane directly into the systemic circulation. The advantages of this route are :

- (i) Rapid onset of action,
- (ii) Quick termination of the drug effect by spitting the tablet,
- (iii) Degradation of the drug in the stomach is avoided.

Further, since the drug enters the systemic circulation, the rapid inactivation of the drug in the liver is avoided.

Drugs commonly administered by sublingual route are nitroglycerin in angina pectoris, buprenorphine as an analgesic and isoprenaline sulfate in bronchial asthma.

(b) **Trans-nasal route** e. g. dDAVP, a synthetic analogue of vasopressin, the hormone of the posterior pituitary gland, is administered by this route. It is important that no poisonous

substance be administered by this route, as it may reach the brain along with lymphatic channels.

(c) **Trans-rectal route** : The rectum has a rich blood and lymph supply and drugs can cross the rectal mucosa like the other lipid membranes; thus, unionized and lipid soluble substances are readily absorbed from the rectum. The portion absorbed from the upper rectal mucosa is carried by the superior haemorrhoidal vein into the portal circulation whereas that absorbed from the lower rectum enters directly into the systemic circulation via the middle and inferior haemorrhoidal veins. The advantages of this route are that gastric irritation is avoided and that by using a suitable solvent the duration of action can be controlled. Moreover, it is often more convenient to use drugs rectally in the long term care of geriatric and terminally ill patients. Administration of a rectal suppository or a capsule is a simple procedure which can be undertaken by unskilled persons and by the patient himself. Examples of drugs that can be given as a rectal suppository are indomethacin in rheumatoid arthritis, aminophylline for bronchospasm and chlorpromazine for vomiting.

V. New drug delivery systems : Various novel drug delivery systems which incorporate drugs in a programmed dosage form, that administers the medication at a predetermined rate, automatically, over an extended period of time from a single application, have been developed. One such system, called *Ocusert*, when placed directly under the eyelid, can deliver a steady flow of pilocarpine round the clock for seven days without causing any discomfort, thus avoiding the need for repeated eye drops. Another device, called *Progestasert*, an intrauterine contraceptive device, produces controlled release of minute quantities of progesterone within the uterus for a year. Similar therapeutic systems are available for transdermal route Estraderm.

Another novel approach to drug delivery involves the use of prodrug. *Prodrug* is an inactive chemical derivative that, after administration, undergoes biotransformation to the pharmacologically active drug. Such prodrug may over-

come the barriers limiting the usefulness of a drug.

The barriers could be in the pharmaceutical phase or pharmacokinetic phase. Thus, propoxyphene napsylate is a tasteless, stable and sparingly soluble derivative of propoxyphene; chloramphenicol palmitate is useful in paediatric practice to reduce the bitter taste of chloramphenicol. Since dopamine does not cross the blood-brain barrier and is easily metabolized, 1-dopa is used to treat Parkinson's disease, to increase the bioavailability of dopamine inside the CNS. Altering the polarity of ampicillin by esterifying ampicillin to form talampicillin improves the bioavailability of ampicillin.

Prodrugs may also be used to achieve longer duration of action e.g. esters of antipsychotic phenothiazines like fluphenazine and of penicillin. Another important use of prodrugs is to provide site-specific delivery of drugs. Thus, methenamine is a prodrug for formaldehyde; it is converted to formaldehyde and ammonia at the acidic urinary pH and is used as a urinary tract antiseptic.

Computerized, miniature, syringe pumps are now available for continuous or intermittent (pulsed) administration of drugs such as insulin and GnRH (respectively) for optimal drug effect.

'Targeted' delivery of anti-cancer drugs using monoclonal antibodies against cancer cell antigens is one of the newer innovations in drug delivery systems. These antibodies 'home in' on the cancer cells and deliver lethal concentrations of the drug selectively to the cancer tissue.

A drug may exert different effects when given by different routes. Thus, oral magnesium sulfate acts as a saline purgative. When injected, it is a depressant of the central nervous system and acts as an anticonvulsant. On the other hand, hypertonic magnesium sulfate, given as a retention enema, can be used to reduce intracranial tension.

ABSORPTION AND BIOAVAILABILITY OF A DRUG

It is important to know the manner in which a drug is absorbed. The route of administration

largely determines the latent period between administration and onset of action.

Drugs given by mouth may be inactive for the following reasons :

(a) Enzymatic degradation of polypeptides within the lumen of the gastrointestinal tract e.g. insulin, adrenocorticotrophic hormone (A.C.T.H.)

(b) Poor absorption from the gastrointestinal tract e. g. aminoglycoside antibiotics.

(c) Inactivation : Compounds like testosterone and aldosterone are absorbed from the gastrointestinal tract but are degraded in the gut wall or during the first passage through the liver before they can reach their site of action.

Pharmaceutical preparations that satisfy the chemical and physical standards laid down in pharmacopoeia (*chemically equivalent*) may not necessarily yield similar concentrations of the drug in the blood or the tissues (*biologically non-equivalent*) and thus may not provide equal therapeutic benefits (*therapeutic non-equivalence*). Bioavailability of a drug (availability of biologically active drug) is defined as the amount or percentage of drug that is absorbed from a given dosage form and reaches the systemic circulation following non-vascular administration. When the drug is given I.V., the bioavailability is 100%. This may not be so after oral administration.

Factors affection drug absorption and its bioavailability are :

1. Physical properties of drug.
2. Nature of the dosage form.
3. Physiological factors.

Physical properties :

(a) *Physical state* : Liquids are better absorbed than solids, and crystalloids are better absorbed than colloids.

(b) *Lipid or water solubility* : High lipid solubility of the unionised drug favours its absorption from the gastrointestinal tract. Bile salts assist the absorption of the fat-soluble vitamins from the small intestine.

Dosage forms :

(a) *Particle size* : The particle size of sparingly soluble drugs can affect their absorption. Thus, a

tablet that contains large aggregates of the active compound does not disintegrate easily even on prolonged contact with gastric and intestinal juices and hence, is poorly absorbed. Small particle size is important for absorption of corticosteroids, antibiotics like chloramphenicol and griseofulvin, certain oral anticoagulants, tolbutamide and spironolactone. Thus, the dosage of the active drug can be reduced without lowering efficacy simply by reducing the particle size. On the other hand, in case of an anthelmintic such as bephenium hydroxynaphthoate, the particle size should be large enough to reduce its absorption, thus making the treatment more effective and less toxic. Drugs given in a dispersed or emulsified state are absorbed better e.g. vitamin D and vitamin A.

(b) *Disintegration time and dissolution rate* : The effect of the physical factors is commonly evaluated by determining (i) the 'disintegration time' which measures the rate of break up of the tablet of the capsule into the drug granules; and (ii) the 'dissolution rate' which is the rate at which the drug goes into solution. The disintegration time of a tablet is a poor measure of the bioavailability of the contained drug. This is so because, in addition to disintegration time and particle size, various other factors such as crystalline form (polymorphism), saturation solubility and solvation can modify the bioavailability of a drug. The dissolution rate is perhaps a better parameter.

(c) *Formulation* : Usually, substances like lactose, sucrose, starch and calcium phosphate or lactate are used as inert diluents in formulating powders or tablets. Such fillers may not be totally inert but may affect the absorption as well as stability of the medicament. Thus, calcium and magnesium ions reduce the absorption of tetracyclines, while calcium phosphate used as a diluent for calciferol may cause calcium toxicity, when given in large doses. Replacement of calcium phosphate by lactose made a marked difference in the efficacy of a reformulated phenytoin preparation. It is well established that the method of formulation can markedly influence the drug absorption and thus determine its bioavailability. A

faulty formulation can render a useful drug totally useless therapeutically. The study of the influence of formulation on the therapeutic activity of drugs is known as 'biopharmaceutics'.

Physiological factors:

(a) *pH of the gastrointestinal fluid and the blood*: This is discussed below.

(b) *Ionization*: It may be assumed for all practical purposes that the mucosal lining of the gastrointestinal tract is impermeable to the ionized form of a weak organic acid or a weak organic base. The organic weakly acidic and basic drugs exist in two forms: 1. an unionized component, predominantly lipid soluble, absorbed rapidly; and 2. an ionized and often water soluble component, absorbed poorly. The unionized fraction can cross the cell membrane which contains lipid, and the amount of the drug which crosses the gut wall is determined by the gradient of its concentration between the lumen of the gut and the portal venous blood. If the plasma concentration of a drug present in a free, unionized form is rapidly reduced by binding with plasma proteins, the drug absorption from the gut lumen is enhanced e.g. salicylate.

Acidic drugs are rapidly absorbed from the stomach. These drugs exist in the acidic medium of the stomach in an unionized form which favours their absorption. These drugs act rapidly

on oral administration e.g. salicylates and barbiturates.

Basic drugs are not absorbed until they reach the alkaline environment of the small intestine. The alkaline environment, in which the major component of the drug exists in an unionized form, facilitates their absorption. The actions of these drugs are delayed when they are administered orally e.g. pethidine and ephedrine.

At the pH values found in the intestine, the strongly acidic or basic drugs are highly ionized and hence they are poorly absorbed. Streptomycin, neomycin, sulfaguanidine, mecamlamine are all strong bases and consequently, their absorption from gastrointestinal tract is poor and irregular.

(c) *G.I. transit time*: The presence of food, and the volume, viscosity and tonicity of the gastric contents can influence drug absorption by altering the gastric emptying time. Rapid absorption occurs if the drug is given before meals. However, certain irritant drugs like the salicylates and the iron salts are deliberately administered after food to minimize the gastrointestinal irritation.

Increased peristaltic activity, as in diarrhoea, reduces the drug absorption. Anti-cholinergic drugs, which prolong gastric emptying time, also impair absorption of drugs. Structural changes in the absorbing mucous membrane result in malab-

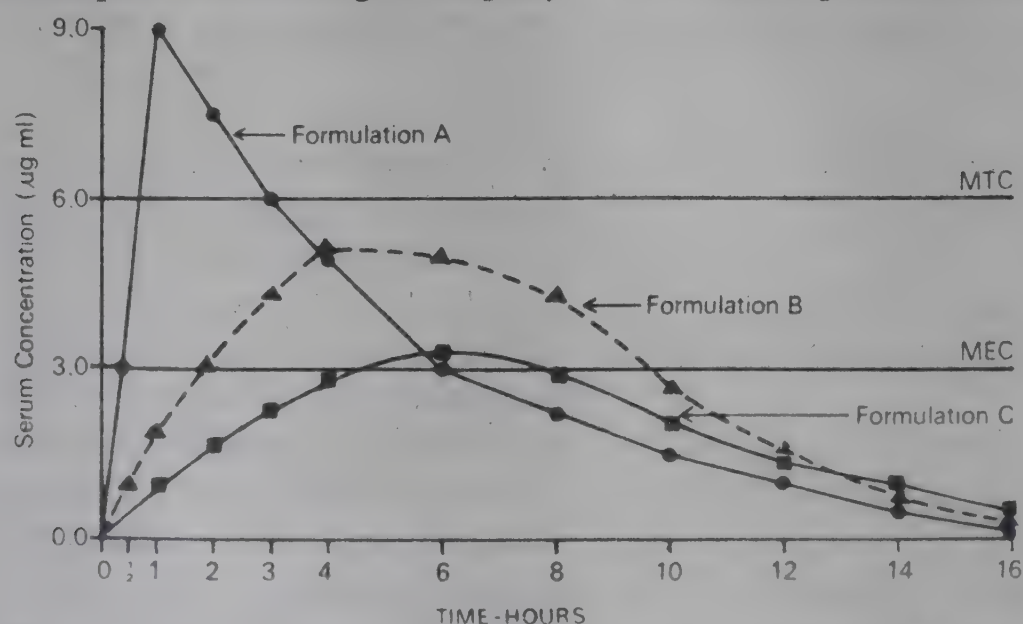


Fig. 1.1 : The plasma drug level curves following administration of three formulations of the same basic drug. MTC = minimum toxic concentration, MEC = minimum effective concentration. For formulations A and B, the areas under the curves are identical. However, formulation A would produce quick onset and short duration of action compared to formulation B whose effect would last much longer. Formulation C gives inadequate plasma levels and is, therefore, likely to be therapeutically ineffective.

sorption syndrome. Gastrointestinal mucosal edema significantly depresses the absorption of drugs such as hydrochlorothiazide in patients with congestive cardiac failure.

(d) *Presence of other agents* : Vitamin C enhances the absorption of iron from the gastrointestinal tract, while phytates retard it. The absorption of fat-soluble vitamins is reduced in the presence of liquid paraffin, whereas cholesterol absorption is reduced by sitosterol. Calcium, present in milk and in antacids, forms insoluble complexes with the tetracycline antibiotics and reduces their absorption.

(e) *Enterohepatic cycling* : This increases the bioavailability of a drug e. g. phenolphthalein.

(f) *Area of the absorbing surface and local circulation* : Drugs can be absorbed better from the small intestine than from the stomach because of the larger surface area of the former. Reduction in the area of the absorbing surface as following major gastrointestinal surgery, reduces the drug absorption. Increased vascularity can increase absorption.

(g) *Metabolism of drug* : Rapid degradation of a drug by the liver during the first pass (as in the case of propranolol) or by the gut wall (as in the case of isoprenaline) also affects the bioavailability. Thus, a drug, though absorbed well when given orally, may not be effective because of its extensive first pass metabolism.

(h) *Pharmacogenetic factors* : These are discussed later.

(i) *Disease states* : Absorption and first pass metabolism may be affected in conditions like malabsorption, thyrotoxicosis, achlorhydria and cirrhosis of the liver.

The only valid tests of bioavailability of a drug preparation are (a) the plasma level or urinary excretion of the drug, and (b) an objectively measurable parameter of its therapeutic efficacy.

Single dose bioavailability test involves an analysis of plasma or serum concentration of the drug at various time intervals after its oral administration and plotting a serum concentration-time curve (Fig. 1.1). The area under such a curve

(AUC) provides information about the amount of drug absorbed along with the rate of absorption and the time required to achieve the maximum concentration (T_{max}), following drug administration. The bioavailability F is determined by comparing the AUC after oral administration of a drug with the AUC after intravenous administration of the same dose of the drug.

$$F = \frac{\text{AUC after oral dose}}{\text{AUC after I.V. dose}}$$

The determination of bioavailability is a time consuming and expensive procedure and needs to be carried out only in the case of life saving drugs and drugs with a narrow therapeutic index.

Absorption of a drug from various mucosae and its distribution within the cell is modified by a series of membranes. In the case of the gut the mucosa is many cells thick. The main barrier to the drug transport seems to reside in the cell membrane. Studies of the permeability of this membrane suggest that a lipid barrier is present. Although the membrane also contains pores, only small water soluble molecules can pass through them.

Absorption of drugs from the gut occurs by :

(a) *Simple diffusion* : This is a bidirectional process where the rate of transfer across a membrane is proportional to the concentration gradient. A water soluble drug of low molecular weight such as alcohol or urea and water itself diffuse passively through aqueous pores of the membrane. Water soluble drugs with larger molecular weight do not cross the membrane passively but need an active transport process for absorption. Drugs which are lipid soluble, however, are mostly transferred by simple or passive diffusion after first dissolving in the lipid of the cell membrane. Highly lipid soluble drugs can thus be absorbed by this process regardless of the pH of the medium, provided the drug is able to dissolve sufficiently in the intestinal fluid and reach the absorptive surface.

(b) *Active transport* : This is a specialized

process requiring energy and is independent of the physical properties of the membrane. Drugs with large molecular size need an active transport system to assist their absorption. A few synthetic drugs are absorbed by active transport because of structural similarity to natural substances e.g. alpha methyl dopa, an analogue of phenylalanine. Drugs related to steroids, glucose, and amino acids may be absorbed by active processes that are normally involved in the absorption of dietary and endogenous substances. Majority of the drugs are not absorbed by active transport. *Carrier transport* is an active transport where a carrier molecule combines with a drug to be transported at one membrane surface and dissociates from it at another surface e.g. intestinal absorption of calcium.

(c) **Pinocytosis** : Another process which plays an important role in unicellular organisms like amoeba is pinocytosis, where the cell takes up from its surroundings fluid or macromolecules but not particulate matter. The significance of the phenomenon in multicellular organisms, however, is doubtful.

As a rule, drugs which are neither lipid nor water soluble e.g. barium sulfate, are not absorbed from the gut.

Information regarding the rate of absorption is necessary:

(i) to determine the frequency of administration, (ii) to ascertain the duration of effective action and (iii) to predict the onset of desired or undesired effects of the drug.

The time between the administration of a drug and the development of response is known as the *biological lag*.

DISTRIBUTION OF A DRUG

After absorption, a drug enters or passes through the various body fluid compartments such as (a) Plasma, (b) Interstitial fluid compartment, (c) Transcellular fluid compartment e.g. fluids in the gastrointestinal tract, bronchi, C.S.F. and (d) Cellular fluid compartment.

Every drug is distributed throughout the body in a characteristic manner, depending upon its physicochemical properties. The apparent volume of distribution (V_d) is calculated as the total amount of drug in the body divided by the concentration of the drug in the plasma at zero time. For many drugs, (V_d) is constant over a wide dosage range.

Some drugs pass into the cell, some remain on the cell membrane and some may be distributed extracellularly. However, a drug can penetrate into and exist in more than one compartment. The rate of passage of a drug through a membrane is dependent upon the pH of the drug's environment and the dissociation constant (pK) of the drug, the pH at which the nonionized and ionized drug concentrations are equal. Nonionized, lipid soluble drugs (the vast majority) that readily cross membranes are distributed throughout the body; they have large volumes of distribution. On the other hand, drugs which are highly protein bound (e.g. warfarin) remain largely within the vascular compartment and have low volumes of distribution (6-7 litres). Where the V_d exceeds the total volume of body water (42 litres), there is substantial uptake and binding of the drug within tissues such as muscle and brain.

Plasma concentration of a drug : This depends upon the rate of absorption, distribution, metabolism and excretion of the drug.

After absorption, the drug circulates in the blood either in the free form or bound to plasma proteins. The fraction bound to protein usually falls as the total concentration of the drug is increased and the binding sites become saturated.

Binding of drugs to plasma proteins assists absorption. Diffusion across the intestinal wall continues as long as the concentration within the gut exceeds that of the unbound fraction in the portal capillaries.

Protein binding acts as a temporary 'store' of a drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids.

Protein binding reduces diffusion of the drug into the cell and thereby delays its metabolic

degradation e.g. 90 per cent of long-acting sulfonamides and 96 per cent of phenylbutazone circulate in bound form while protein binding is negligible with antipyrine. Protein binding also reduces the amount of drug available for filtration at the glomeruli and hence delays its excretion. Clearance is the volume of plasma cleared of the drug by metabolism and excretion per unit time. Protein binding thus reduces the clearance of a drug.

The extent of drug binding depends on the binding protein concentration in the plasma. Thus, in pregnancy, the protein bound fraction of substances such as thyroxine increases due to a rise in the concentration of the specific binding protein in the plasma. Conversely, in hypoproteinaemia, there is a rise in the free fraction due to low plasma protein levels; the therapeutic dose required may thus be smaller.

Since it is the diffusible portion of the drug which determines its activity, with highly protein bound drugs like long-acting sulfonamides, the concentration may be too low in interstitial fluid, cerebrospinal fluid and tissue cells to combat dangerous infections.

While prescribing any new drug such as an antibacterial agent claimed to achieve higher and longer plasma concentration than a previously available drug, one should ascertain the degree of protein binding. With extensively protein bound drugs, the therapeutic activity may be low.

Administration of drugs which get bound to the same binding sites on plasma proteins may result in a sudden increase in the free concentration of one of them, possibly to a dangerous level. Thus, if a patient, stabilised on an anticoagulant like phenindione, takes salicylates in addition, a sudden increase in free concentration of phenindione can occur due to its displacement from the binding sites by salicylates. This may result in haemorrhage. See also Chapter 2.

Drug storage : The concentration of a drug in certain tissues after a single dose may persist even when its plasma concentration is reduced to low or undetectable levels. Thus, the hepatic concentra-

tion of mepacrine within 4 hours after its oral administration is 200 times that of plasma level. This concentration may reach a very high level on chronic administration. Iodine is similarly concentrated in the thyroid tissue.

Many lipid soluble drugs are stored in the body fat depots e.g. on intravenous administration, 70 per cent of the barbiturate thiopentone, is taken up by the body fat from which it is released slowly. Because of such storage, repeated exposure to certain chemicals (e.g. D.D.T) even in small doses may lead to chronic toxicity.

Although termination of drug effects mainly occurs due to biotransformation and excretion, it may also result from redistribution of the drug from its site of action into other tissues or sites.

Placental transfer : Many drugs pass through the placenta into the fetal circulation. Such passage is determined by the properties of the drug, the evolving properties of the placenta and the altered maternal blood levels as dictated by the changing pharmacokinetics of pregnancy. The effect on the fetus is determined by the stage of the fetal life, among other factors. Details of the drug use during pregnancy are discussed in Chapter 72.

FATE OF THE DRUG

The changes that a drug undergoes in the body and its ultimate excretion are considered as the fate of the drug. Alteration of a drug within a living organism is known as *Biotransformation*.

After absorption, drugs could undergo three possible fates, namely, they could be metabolized by enzymes, they could change spontaneously into other substances without the intervention of enzymes, or they could be excreted unchanged. Some drugs such as mechlorethamine (a nitrogen mustard) change spontaneously into other compounds simply because of appropriate pH of body fluids.

The metabolism of drugs usually tends to make the less polar, lipid soluble substances more polar and water soluble, thus facilitating their excretion

by kidneys. If a drug is already highly polar and water soluble then it may not get metabolized and may get excreted as such. Many, but not all, of the drugs, such as decamethonium and methotrexate, which are not readily metabolized are highly polar.

Majority of the drugs, however, are metabolized by the enzymes resulting in their activation, inactivation or modification. The reactions which bring about these changes are:

- (a) oxidation.
- (b) reduction.
- (c) hydrolysis, and
- (d) synthesis (conjugation or transfer reactions).

Oxidation, reduction and hydrolysis introduce polar groups such as hydroxyl, amino, sulfhydryl and carboxy into drugs which are consequently made water soluble and pharmacologically less active. Thus, metabolism of drugs is essentially a detoxication process. However, during the initial stages of metabolism of certain drugs active and even toxic compounds may be produced. Thus, parathion, an insecticide, is quite inactive in itself but is converted in the body to paraxon, the active toxic compound; similarly, imipramine, an anti-depressant drug is transformed in the body into an active compound desmethylinipramine; cyclophosphamide, sulindac and enalapril are activated by oxidation as the first step.

There are many tissues which can metabolize drugs, but by far the most active tissue per unit weight is the liver. The enzymes which metabolize drugs are distinct from those which function in the intermediary metabolism. However, they also metabolize the steroid hormones. These enzymes are located in the liver microsomes, which form a part of the smooth membrane of the endoplasmic reticulum of the hepatic cells. The microsomes are obtained as a sediment when the liver cells are homogenized and then subjected to high speed centrifugation. Among these enzymes are esterases, amidases, glucuronyl transferases and others that catalyze a variety of oxidative and reductive reactions. Microsomal enzyme systems

are accessible only to substances with a high oil/water partition coefficient. These enzymes alter drugs mainly to make them more water soluble, so that they can be excreted by the kidneys. Animal species vary not only in the kinds of microsomal enzymes they possess but also in their quantitative distribution.

The ability of the microsomal enzymes to metabolise drugs is poor in premature infants and neonates as compared to adults. Chloramphenicol is conjugated with glucuronic acid in the adult liver and only 10 per cent is excreted unchanged in the urine. The liver of a premature infant is unable to conjugate chloramphenicol to the same extent as in adults and this may result in very high serum concentration of chloramphenicol in the infant, which may prove highly toxic. Undernutrition also depresses the functional capacity of these enzyme systems and this should be borne in mind particularly in poor developing countries where undernutrition is common.

Certain drugs like barbiturates, on repeated administration, stimulate the microsomal enzyme systems. This is called *enzyme induction* and it accelerates the biotransformation of drugs. Exposure of several animal species to the insecticide DDT accelerates the biotransformation of a variety of drugs, thus promoting their faster elimination. Enzyme induction also occurs to a limited extent in kidney, lung, skin, gut and plasma.

Apart from species and strain, other factors such as age, sex, genetic endowment, diet, route of administration, duration of administration, simultaneous administration of other drugs and disease can influence drug metabolism. The sumtotal of these interlinked factors makes a single-dose regimen with lipid soluble drugs unrealistic.

Drugs are also metabolized by enzymes which are of non-microsomal origin, present in liver, plasma and tissues including placenta and even by those present in the intestinal micro-organisms (microfloral enzymes).

Oxidation : Microsomal oxidation may involve the introduction of a hydroxyl group into the drug molecule (hydroxylation) e.g. conver-

sion of salicylic acid to gentisic acid, or an alkyl or amino group may be removed e.g. conversion of phenacetin to the active compound p-acetaminophenol (dealkylation) or of amphetamine to benzyl-methyl-ketone (deamination). A drug may be oxidized by more than one mechanism and for the same drug this may differ in different species of animals.

Oxidation can also be catalysed by non-microsomal oxidative enzymes. Thus, ethyl alcohol is oxidized to carbon dioxide and water. Methyl alcohol is oxidized to formic acid and formaldehyde. Formaldehyde may damage the optic nerve and can produce metabolic acidosis; because of this toxic nature, methyl alcohol is used to 'denature' spirit.

A mitochondrial enzyme monoamine oxidase (MAO) causes oxidative deamination of substances like adrenaline, 5-HT and tyramine.

Reduction : Many halogenated compounds and nitrated aromatic compounds are reduced by the microsomal enzymes e.g. halothane, chloramphenicol, and prontosil; drugs like chloral hydrate and disulfiram are reduced by non-microsomal enzymes.

Hydrolysis : This is usually carried out by enzymes 'esterases' that hydrolyse (split with addition of water) the esters. These enzymes are microsomal, non-microsomal and microfloral in origin. They are usually of low specificity and exhibit considerable species variation. Drugs like pethidine, procaine, acetylcholine, diacetylmorphine, atropine, neostigmine and phenytoin, are hydrolysed by esterases. Digitalis glycosides are rendered inactive by hydrolysis.

Hexamine is hydrolysed in the urinary tract, at an acid pH, to formaldehyde and ammonia; formaldehyde exerts an antibacterial action in the urinary tract.

Conjugation or transfer reaction : This is a synthetic process by which a drug or its metabolite is combined with an endogenous substance, resulting in various conjugates such as glucuronides, ethereal sulphates, methylated compounds and amino acid conjugates. Conjugation

invariably results in inactivation of the compound. After such inactivation, large molecules are eliminated in the bile whereas smaller molecules ($MW < 300$) are excreted in the urine.

Glucuronides are produced by the combination of a hydroxyl, carboxyl or amino group of drug molecule with glucuronic acid. Ethereal sulphates are produced by the combination of sulphate and hydroxyl or amino group.

Phenobarbitone is oxidised to its hydroxy derivative which is conjugated with glucuronic acid. Compounds like morphine, paraamino benzoic acid (PABA), stilboesterol, salicylic acid and phenol are excreted mainly in the form of glucuronides. A classical example of amino acid conjugation is the combination of benzoic acid with glycine to form hippuric acid.

A drug may be metabolized and inactivated by more than one successive reaction e.g. progesterone is first reduced to pregnanediol which is then conjugated; chloramphenicol is similarly reduced and then conjugated.

The ability of the diseased liver to metabolise drugs diminishes. Drugs like pethidine and morphine which are metabolized in the liver may thus have an unusually prolonged action in the liver cirrhosis.

DRUG EXCRETION

Drugs, except the volatile general anaesthetics, are usually excreted by a route other than that of absorption. The important channels of drug excretion are :

Kidneys : The processes which contribute to the elimination of a drug in the urine are :

(i) passive glomerular filtration, (ii) active tubular secretion, and (iii) passive diffusion across the tubules.

Unionized drugs which are well absorbed are filtered at the glomerulus, but they can diffuse back from the lumen of the renal tubule into the cells lining the tubules. Thus, ultimately a very small amount of the drug appears in the urine.

Ionized drugs which are poorly absorbed are

excreted almost entirely by glomerular filtration and are not reabsorbed.

Many weak acids such as penicillin, cephalosporins, salicylate, probenecid, thiazides, amiloride, cimetidine and procainamide are transported across the renal tubules by systems responsible for the transport of naturally occurring substances such as uric acid i.e. they are actually secreted in the urine. Weak bases are also secreted into the tubular lumen.

Passive diffusion is a bidirectional process and drugs may diffuse across the tubules in either direction depending upon the drug concentration and the pH e.g. mepacrine and salicylates.

In the presence of renal damage, the ability of the kidney to excrete drugs is impaired. This might result in high blood levels and prolonged drug action with normal doses. Great care must, therefore, be exercised when drugs like aminoglycosides or coumarin anticoagulants are used in the presence of impaired renal function. Similarly, potassium salts may produce dangerous hyperkalemia if the kidney function is inadequate. (For calculation of doses of drugs in chronic renal failure, see Chapter 46.)

Protein binding reduces the amount of the drug available for filtration at the glomerulus but protein bound drugs may still be available for secretion by the proximal renal tubules e.g. phenylbutazone. This is because the bound form of the drug is released from its combination with plasma proteins when the plasma concentration of the free form of the drug is lowered.

Most of the acidic and the basic drugs are secreted by the renal tubules (see above). Tubular secretion of weak organic acids such as penicillin can be blocked by probenecid and their half-life can be prolonged. Secretion of weak bases by renal tubules can also be blocked but the blocking agents are too toxic for any therapeutic utility.

The pH of the urine influences the excretion of certain weak acids and bases. Thus, weak acids are quickly eliminated in an alkaline urine e.g. barbiturates and salicylates; while weak bases are rapidly excreted in an acidic urine e.g. pethidine,

mecamylamine, and amphetamine. On the other hand, the action of these substances in the body can be prolonged if the urinary pH is not favourable for their excretion.

The tubular reabsorption of weak acids is minimum when the urine is alkaline because a large portion of these compounds is ionized in an alkaline medium. Similar is the case with weak bases in acid urine. Elimination of weak acids and bases can thus be accelerated by maintaining a high rate of urine flow by the use of compounds like mannitol and diuretics and by adjusting the urinary pH.

The rate of renal excretion of a drug may vary in different species. Thus, phenylbutazone excretion in man is slow, while in mice, rabbits, dogs and guinea pigs, the same drug is excreted rapidly and hence, it disappears from the blood within a few hours.

Lungs : Volatile general anaesthetics and certain other drugs like paraldehyde and alcohol are partially excreted by the lungs. The presence of paraldehyde and alcohol can be recognised by the odour they impart to the breath.

Skin: Metalloids like arsenic and heavy metals like mercury are excreted in small quantities through the skin. Arsenic gets incorporated in the hair follicles on prolonged administration. This phenomenon is used for detection of arsenic poisoning.

Bile : Drugs such as novobiocin and erythromycin are excreted in the urine only in small amounts but appear in high concentrations in the bile. Another drug which is excreted in bile is the purgative phenolphthalein. Such drugs may get repeatedly reabsorbed from the jejunum and reexcreted in bile, thereby exerting a prolonged action (Enterohepatic circulation).

Intestines : Purgatives like cascara and senna which act mainly on the large bowel are partly excreted into that area from the blood stream after their absorption from the small intestine. Heavy metals are also excreted through the intestine and can produce intestinal ulceration.

Milk and saliva : Secretion of drugs in milk is

discussed in Chapter 72.

Certain drugs like iodides and metallic salts are excreted in the saliva. Lead compounds deposited as lead sulfide produce blue line on the gums. Excessive salivation is a frequent symptom of chronic, heavy metal poisoning.

Many drug-eliminating mechanisms, such as biliary and renal tubular secretion and biotransformation, are capable of saturation. This is discussed below.

BIOLOGICAL HALF-LIFE AND ITS SIGNIFICANCE

Information about the time course of drug absorption, distribution and elimination (Pharmacokinetics) can be expressed in mathematical terms and has an important role in understanding and planning drug regimes. Pharmacokinetic principles aid in the selection and adjustment of drug dose schedules. *However, they are not a substitute for, but rather a supplement to, clinical monitoring and judgement.*

Elimination of most drugs occurs exponentially (*first order kinetics*) i.e. a constant fraction of the drug in the body disappears in each equal interval of time. In most instances, the rate of disappearance of a drug from the body is reflected in the rate of lowering of its plasma concentration. Thus, following a single intravenous dose, the plasma concentration of the drug is found to fall exponentially. Thus, the drug is removed from the body not at a constant rate but at a rate proportional to its plasma concentration. In the case of an exponentially eliminated drug, a plot of the log of concentration against time gives a straight line. The rate of an exponential process may be expressed either in terms of its rate constant (K) which expresses the fractional change per unit of time, or in terms of its half time ($t/2$) the time required for 50% completion of the process (*elimination half-time, plasma half-life or biological half-life*). With drugs whose elimination is exponential, the biological half-life is independent of the dose, the route of administration

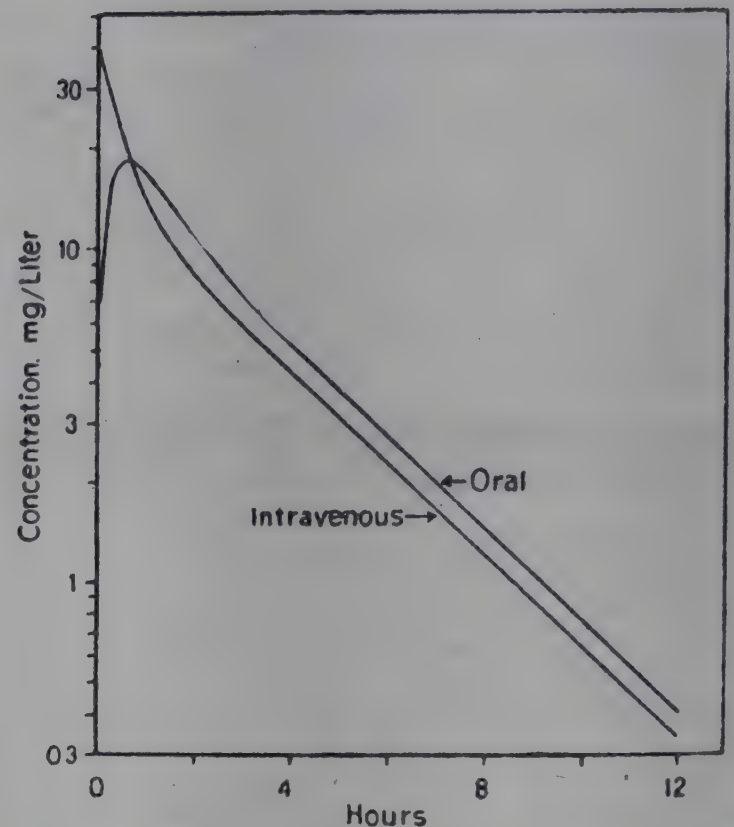


Fig. 1.2 (a) : Exponential curves of plasma concentration of a drug following oral and I.V. administration. The slope is independent of the route of administration (First order kinetics)

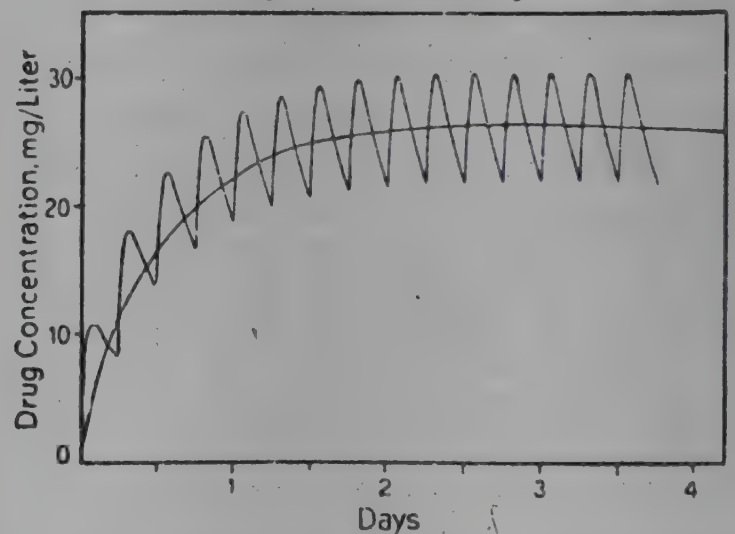


Fig. 1.2 (b) : Rise of drug concentration to a plateau (steady state) level during repeated oral administration of a constant dose.

and the plasma concentration. It depends on V_d as well as on the metabolism and the renal excretion of the drug. However, the actual quantity of the drug removed per unit time is smaller at lower plasma concentrations and larger at higher plasma concentrations. Further it should be noted that $t/2$ during long term administration of a drug may be different from that after intravenous administration of single doses. Reduced elimination of the drug causes prolonged biological half-life and

prolongation of the drug effect.

Simple calculation shows that 93.75 per cent of the drug is eliminated after four-half times. Since more than four half-times are required for complete exponential elimination, repeated administration of a drug at intervals shorter than this leads to drug accumulation. Under these circumstances a drug administered in equal doses, intermittently, at constant time intervals, will accumulate exponentially to a plateau plasma level. After the plateau is reached, drug elimination equals drug absorption during the dose interval. The time taken to attain the plateau depends only upon the accumulation half-time of the drug which equals its biological half-life. Thus, it takes about four biological half-lives for the drug to reach the plateau level in the plasma. However, the drug concentration maintained during the plateau state is directly proportional to both biological half-life and the quantity of the drug given per unit time (expressed as dose/dosage interval).

When a drug is administered repeatedly in the same dose at fixed, long intervals of time, marked fluctuations in the plasma concentration (during plateau state) may occur between the doses in the case of a drug with rapid absorption or short biological half-life. These fluctuations can be reduced by giving the drug at shorter intervals, say by giving half doses at half intervals. Thus, during levodopa therapy, steady plasma levels and a steady clinical response can be maintained only by giving the drug in at least four divided doses per day. To mention an extreme case, insulin with half life of a few minutes is best administered by a continuous, intravenous infusion for maximum efficacy in diabetic coma. On the other hand, with drugs with long half-lives these fluctuations in the plasma concentration at plateau are less marked and hence these drugs may be administered at longer intervals. Thus, for maintenance therapy, digoxin, thyroxine and reserpine may be given once a day to maintain a steady response.

In the case of some drugs (human growth hormone and propranolol), the pharmacological effects may in fact last much longer than is suggested by their $t_{1/2}$. With some drugs (e.g. al-

lopurinol) this may be due to the formation of an active metabolite (e.g. oxypurinol). Such drugs can therefore be given at much longer intervals than their $t_{1/2}$ would indicate.

In order to prevent unduly high plasma levels of a drug when its elimination is reduced in a patient with impaired hepatic, renal or cardiovascular function, the maintenance dose must be reduced either by reducing each individual dose or by lengthening the dosage interval in proportion to the increase in the biological half-life.

Most of the drugs are eliminated exponentially (first order kinetics) throughout the entire dosage range. However, with certain drugs such as phenytoin, dicoumarol, probenecid, oral propranolol, large doses of salicylates, phenylbutazone, alcohol and, in some patients, aminophylline, the elimination is exponential with lower dosage levels; but when the dose exceeds a certain critical level, the eliminating mechanisms get saturated and then a fixed quantity of the drug is eliminated per unit time. This is called 'dose dependent elimination' or 'saturation kinetics' or '*zero order kinetics*'. With such drugs, an increase in the dose can cause an increase in the biological half-life and a disproportionate increase in the plasma level. This can result in drug toxicity.

The therapeutic response to some drugs correlates better with plateau plasma levels than with dosage. Further, these drugs have a low therapeutic index. Hence, plasma concentrations of drugs such as theophylline, lithium, aminoglycosides, digoxin, antiarrhythmic agents and antiepileptic drugs can be reliable guide to therapy provided they are interpreted in concert with the clinical information. It should be remembered that people differ in the rate at which they metabolize drugs. With drugs such as tricyclic antidepressants and phenytoin, there may be as much as 3-5 fold variation in the plasma concentration achieved in different individuals given similar doses. Further, drug concentration in certain tissues may persist longer even when the plasma drug concentration is low or undetectable after stopping the drug, thus giving a prolongation of the effect e.g. phenothiazines in neuronal endings and digitoxin in

the ventricular muscle.

METHODS OF PROLONGING THE DURATION OF ACTION OF A DRUG

The drug action can be prolonged by :

- (a) Retarding drug absorption.
- (b) Inhibiting drug metabolism in the liver.
- (c) Slowing renal excretion of the drug.
- (d) Using compounds which are highly protein bound.

Retarding drug absorption : Absorption of a drug after oral administration can be retarded by administering it on full stomach or by giving it in an enteric coated form. This, however, does not necessarily prolong the action of a drug.

Absorption of a drug after parenteral administration can be retarded by :

(i) *Reduction in the vascularity of the absorbing surface :* This can be achieved by administration of a vasoconstrictor compound along with the drug, e.g. adrenaline with procaine. The same effect may also be produced by applying a tourniquet.

(ii) *Reduction in the solubility of the drug :* This can be achieved by combining the drug with a compound having poor water solubility or giving the drug in a suspension form. Thus, penicillin is combined with procaine, a compound with poor water solubility; aqueous suspension of testosterone also has a prolonged action.

(iii) *Administration of the drug in oily solution or in combination with bee's wax :* e.g. pitressin tannate in oil and adrenaline in oil. Mixing of the drug with a water repellent like aluminium monostearate also delays the absorption, as in the case of penicillin with aluminium monostearate.

(iv) *Combination of the drug with a protein* from which it is released slowly e.g. insulin is combined with protamine in the preparation protamine zinc insulin.

(v) *Esterification :* Sex hormones such as testosterone and estrogens, when esterified with carboxylic acids, such as benzoic acid and propionic acid, give compounds which are absorbed

slowly, thus prolonging the action. The longer the carbon chain of the carboxylic acid, the more fat soluble the ester becomes, and hence the longer is the action.

(vi) *Implantation of pellets* (e.g. DOCA in Addison's disease) *or of steroid filled silastic capsules* (e.g. testosterone in male hypogonadism and progestogens for contraception). These ensure slow and prolonged absorption.

For ocusert, progestasert and adhesive units, see earlier.

Inhibiting drug metabolism in the liver: The microsomal enzyme systems concerned with biotransformation may be depressed by certain drugs, such as monoamine oxidase inhibitors. Reduced biotransformation leads to prolonged drug action. However, these drugs are not free from toxic manifestations and depression of biotransformation may alter the *milieu interior* of the body by delaying the inactivation of endogenous products like the steroid hormones. This approach, therefore, has no practical application.

Slowing renal excretion of the drug: Excretion of the drug by glomerular filtration cannot be blocked or slowed without producing harmful effects on the kidney, but the tubular secretion of certain compounds can be blocked by employing compounds which share the same tubular secretory pathway. Thus, probenecid and para amino hippuric acid have been used to reduce the penicillin excretion.

Increased protein binding of the drug in the plasma : Long-acting sulfonamides like sulfamethoxypyridazine are bound to the plasma proteins much more extensively than short-acting sulfonamides like sulfadiazine. Another compound, suramin, used in the treatment of trypanosomiasis, is extensively and firmly bound to the plasma proteins and hence, has a prolonged action.

SITE OF DRUG ACTION

The site of drug action or where a drug acts, and

the mechanism of drug action or how the drug acts, are the two most fundamental and yet most complex problems in pharmacodynamics. The inadequacy of our knowledge can be attributed to the insufficient information available about the biochemistry and physiology of the cell.

Generalising about the site of drug action is easy and a tentative conclusion can be arrived at by the process of elimination, but the precise determination of the specific site and the mechanism of action of the drug is difficult and often impossible; this is true of many drugs used in therapeutics. A drug may act:

- (a) at the point of application e.g. corticosteroid ointment.
- (b) during transport in the body e.g. osmotic diuretics like mannitol and urea,
- (c) by reflex effects through nerves, e.g. skin irritants like turpentine oil,
- (d) by reaching a definite concentration in a particular tissue, e.g. volatile general anaesthetics like ether, and
- (e) by reaching a definite concentration in a particular cell, e.g. digitalis.

Drugs that act only at the site of application are said to have *local or topical action* while those that act after absorption are said to have a *systemic or general action*.

Methods for localization of seat of action of drugs :

(a) **Anatomical and physiological :** These are essentially surgical procedures. The technic of excision or of ablation is employed. It consists of isolating the organ or tissues at different levels. Claude Bernard was a pioneer in the application of this technic; he demonstrated the site of action of curare in 1887.

Various parts of the central nervous system or other organs are sequentially exposed, effects of drugs by local application are observed and their disappearance confirmed after ablation, to locate the precise site of action. This technic has been extensively used to locate the site of action of emetic and antiemetic drugs.

(b) **Biochemical localization:** The enzyme systems can be isolated in functional condition by means of *in vivo* and *in vitro* technics and the actions of drugs can be conveniently studied e.g. physostigmine and di-isopropyl fluorophosphate (DFP) on cholinesterase.

(c) **Pharmacological localization:** If a drug produces a fall in blood pressure and if this is prevented by prior administration of an antihistaminic, it can be concluded that the drug probably acts in the same place and by the same mechanism as histamine. Use of blocking agents may also suggest the probable site of action of drugs e.g. atropine in the investigation of drugs having cholinergic actions.

(d) **Tracer technics :** These are the modern procedures in which usually one of the atoms present in the drug molecule is made radioactive. The commonly used radioactive labels are ^{14}C , ^3H , and ^{35}S .

The tracer technic is potentially the most accurate one in determining the distribution and the site of action of drugs, but it is difficult to differentiate between the drug and its metabolites and this may create difficulties in interpreting the results.

STRUCTURE ACTIVITY RELATIONSHIP

The activity of a drug is intimately related to its chemical structure. Knowledge about the chemical structure of a drug is useful for :

- (I) Synthesis of new compounds with more specific actions and fewer adverse reactions,
- (II) Synthesis of competitive antagonist and
- (III) Understanding the mechanism of drug action.

(I) **Synthesis of new compounds :** New compounds or drug substitutes may be designed for the following purposes :

(a) **To increase or decrease the duration of action of the original drug or to get a more potent compound :**

(i) Procaine is a drug which produces local anesthesia when infiltrated beneath the skin.

When administered intravenously, it can reduce the rate and the excitability of the myocardium. However, procaine is very rapidly hydrolyzed in the plasma and hence, its cardiac action is too transient for therapeutic application. A compound structurally similar to procaine but resistant to hydrolysis, namely procainamide, was, therefore, synthesized (Fig. 1.3). It is a valuable drug in the treatment of cardiac arrhythmias.

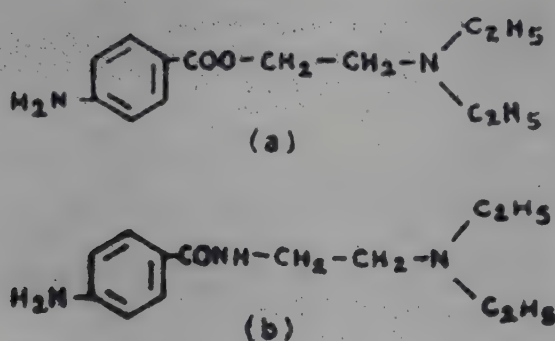


Fig 1.3 : (a) Procaine (b) Procainamide.

(ii) Atropine, when instilled into the eye, produces dilatation of the pupil (mydriasis) and also paralyses the accommodation (cycloplegia). However, the mydriasis and the cycloplegia persist for about a week. Therefore, the substitute homatropine was synthesized (Fig. 1.4). The mydriasis and cycloplegia produced by this compound last for 24 hours.

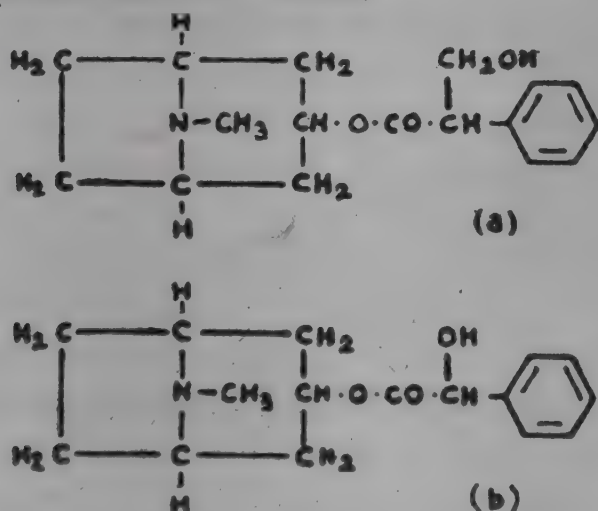


Fig. 1.4 : (a) Atropine. (b) Homatropine

(iii) Diuretic drugs like polythiazide and benndroflumethiazide are as effective as the parent compound, chlorothiazide, in much smaller doses.

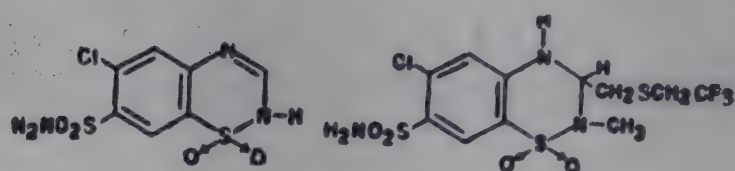


Fig. 1.5 : Chlorothiazide and Polythiazide

(b) To restrict the drug action to a particular system of the body: Chlorpromazine possesses a host of pharmacological actions such as antihistaminic, anticholinergic, hypotensive and antipsychotic. By structural modifications of the chlorpromazine molecule, compounds have been synthesized which have a more potent antipsychotic effect but possess negligible antihistaminic and hypotensive properties e.g. trifluoperazine (Fig. 1.6).

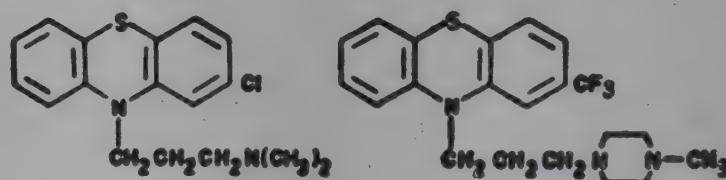


Fig. 1.6 : Chlorpromazine Trifluoperazine

(c) To reduce the adverse reactions, toxicity and other disadvantages associated with the available drugs :

(i) Nicotinic acid used in the treatment of pellagra may produce itching and flushing of the skin and sometimes a fall in blood pressure. A related compound nicotinamide has the same efficacy against pellagra but does not produce itching of the skin or flushing after ingestion.



Fig. 1.7 : Nicotinic acid Nicotinamide

(ii) Benzyl penicillin cannot be administered by mouth as it is inactivated by the hydrochloric acid present in the stomach. Staphylococci develop resistance to this penicillin fairly fast. New penicillins have been synthesized which are not inactivated by the hydrochloric acid in the stomach (and hence can be given by mouth) e.g.

phenoxymethyl penicillin and also those that destroy the staphylococci resistant to benzyl penicillin, e.g. oxacillin (See Chapter 42).

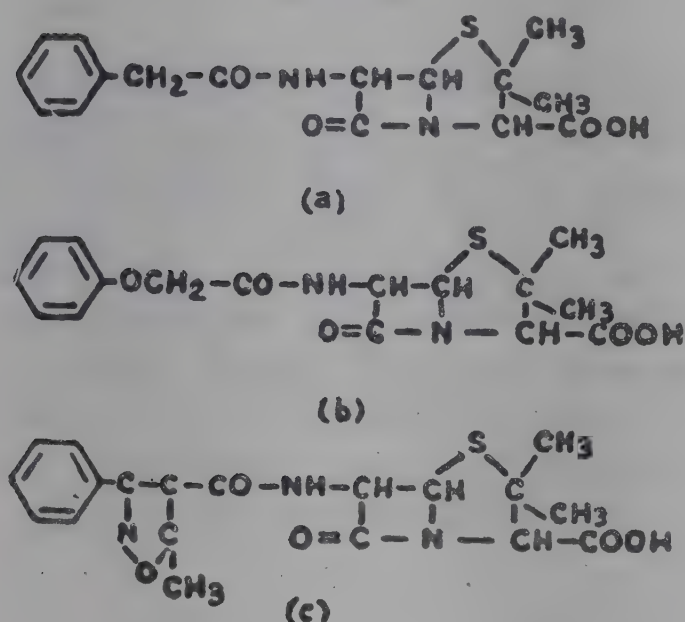


Fig. 1.8 : (a) Benzyl penicillin G
(b) Phenoxymethyl penicillin
(c) Oxacillin

(II) Synthesis of competitive antagonists:

(a) Para-amino benzoic acid is an essential growth factor for several micro-organisms. Para-amino salicylic acid which shows a structural similarity to para-amino benzoic acid probably acts by competing with para-amino benzoic acid for the uptake by certain bacteria. Absence of para-amino benzoic acid ultimately arrests the multiplication of the bacteria (Fig. 1.9).



Fig. 1.9 : PABA

PAS

(b) The respiratory depressant action of morphine can be antagonized by a structurally similar compound nalorphine (See Chapter 8).

(III) Understanding the basic chemical groups responsible for drug action :

(a) The compound adrenaline stimulates

both the alpha and the beta adrenergic receptors. A related compound, isopropylarterenol, selectively stimulates the beta adrenergic receptors while a very closely similar compound dichloroisopropylarterenol (D.C.I.) blocks the beta adrenergic receptors (See Chapter 14).

(b) The drug chlorpromazine (a phenothiazine) is a tranquillizer used commonly in relief of psychotic agitational disorders. A structurally similar compound imipramine (iminodibenzyl derivative), on the other hand, is an antidepressant and is used as a mood elevator (Fig. 1.10).

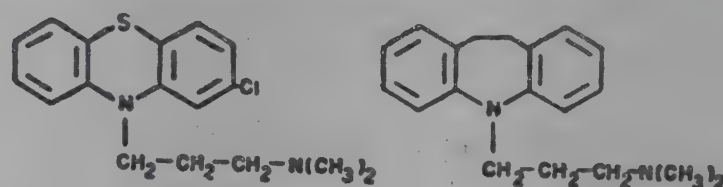


Fig. 1.10 : Chlorpromazine

Imipramine

These examples emphasize the importance of certain chemical groups for the drug action and also give some idea about their mechanism of action.

DRUG RECEPTORS

Some drugs act by combining with ions or small molecules (e.g. neutralization of gastric acid by antacids or chelation of iron by desferroxamine in the treatment of iron poisoning), or by a non-specific effect on the cell membrane (e.g. local anaesthetics). However, the majority of drugs are believed to interact with macromolecular components of tissues called *receptors*. As early as 1905, Langley introduced the idea of a specific 'receptor substance' to explain the action of nicotine and curare. Since then, it has generally been believed that the action of a drug is evoked by direct contact of the drug with a hypothetical component of the cell termed 'the receptor'. Till recently, the 'receptor' was mainly an operational concept. Recent studies, however, indicate that receptors are proteins or enzymes, and a number of receptors have now been identified by ligand binding techniques using radioactive labelled agents and tissue homogenates.

Although receptors are dynamic in nature they can be regarded as definite structural entities interacting with the active principle. The principal parameters which characterize the interaction between a ligand and a receptor are *selectivity* and *affinity*. The selectivity of binding of drugs to receptors is specific and implies a high degree of complementarity in their physico-chemical structures. Thus by studying SAR, information about the receptor sites (receptor mapping) and about those groups (ligands) in the drug molecule essential for binding and/or intrinsic activity can be obtained.

The ability of a drug to get bound to a receptor is termed as the *affinity* of the drug for the receptor. Mathematically, affinity is defined by a constant in the binding relationship between the drug and the receptor. The ability of the drug to elicit a pharmacological response after its interaction with the receptor is termed as the *intrinsic activity* of the drug; another term employed to designate this property is *efficacy* of the drug. To a certain extent, the biological response is regulated by alteration in the receptor numbers and their affinity.

A given drug may act on more than one receptor differing both in function and in binding characteristics e.g. acetylcholine and adrenaline. Further, many factors effect changes in receptor concentration and/or affinity.

A drug which initiates a pharmacological action after combining with the receptor is termed an *agonist*. The agonist, therefore, is essentially a drug with high affinity for the receptor and also high intrinsic activity. Drugs which bind to the receptors but are not capable of eliciting a pharmacological response produce receptor blockade. These compounds are termed *antagonists*. An antagonist, therefore, has the same affinity as the agonist for the receptor but its intrinsic activity is poor. A drug with an affinity equal to or less than that of the agonist but with less intrinsic activity is termed *partial agonist*. Such a drug, no matter how high its concentration, will not produce the full effect which the tissue is capable of. Further, such a partial agonist, because of its ability to

occupy receptors, diminishes the action of an agonist when the two are used simultaneously. In the case of opioids (see Chapter 8), which act on several types of receptors, certain drugs act as agonists or partial agonists on one type of receptor, whereas they act as antagonists on another type of receptor; e.g. pentazocine and nalbuphine act as partial agonists on K receptors but as antagonists on μ receptors. Such drugs are called *agonist-antagonist*.

Recent studies indicate that multiple receptors for a ligand are the rule rather than an exception and that there are 'types' and 'subtypes' of receptors. An important neurotransmitter may activate multiple receptor sites e.g. dopamine has least two specific receptors, histamine can claim three, acetylcholine has four and adrenaline has five.

Increasing concentrations of an agonist evoke a progressively increasing tissue response until the maximum response is reached. If another drug that acts on the same receptor system produces quantitatively different maximum response, then its intrinsic activity must differ. Hence, *differences in maximum response can form the basis for comparing intrinsic activities or efficacy of drugs*.

In practice, this means that drug 'X' can produce a therapeutic effect larger than the maximum effect produced by drug 'Y'. This has great clinical importance. The word *potency* of the drug on the other hand means that weight for weight, drug 'X' has a greater effect than drug 'Y'; the maximum effect obtainable is, however, similar. This hardly matters in clinical practice

The characteristics of drug-receptor interaction could take various forms. In the case of *occupation and activation* model, an agonist, by binding to its receptors site, switches the receptor molecule from non-activated to activated state. With partial agonists only a fraction of the receptors occupied, with competitive antagonists none of the receptors occupied, and with full agonists most (if not all) the receptors occupied, are switched to the activated state.

Some agents are so potent that only a few molecules have to interact with their receptors to

induce a massive response. This obviously needs *an amplifier system*. The simplest amplifier unit is an enzyme molecule that is activated by a drug molecule (active principle) and then converts several substrate molecules into product molecules. If such units are coupled, the product molecules in their turn activate a second enzyme, and so on. Most hormones and neurotransmitters exert their effects without entering the cell. They interact with specific receptors which are coupled to various effector or amplifier systems responsible for generating internal signals or second messengers such as cyclic AMP, cyclic GMP nucleotides and calcium which initiate a further sequence of enzyme reactions. In such *amplifier system model*, the active agent needs to activate only a fraction of its receptors to obtain maximal response from the effector system. Thus, there is a *spare capacity* for the specific receptors.

Sometimes continued exposure to a drug or hormonal agonist leads to a blunted response to that agonist. This phenomenon is termed desensitization, refractoriness or tolerance. It has been demonstrated that desensitization to adrenaline-like drugs is often accompanied by a decrease in the affinity of the receptors for the drug (uncoupling), followed by a decrease in the number of receptors (*down-regulation*). Agonist-mediated desensitization in human tissues has been reported. Thus, the repeated administration of adrenergic agonists like ephedrine in asthmatic patients can down regulate β -adrenergic receptors, resulting in reduced therapeutic response. In contrast to this, depletion of noradrenaline or treatment with adrenergic antagonists lead to a supersensitivity of the tissues to noradrenaline and an *up-regulation* of the adrenergic-receptor number. Thus, chronic administration of β -adrenergic blocker, propranolol, has been shown to be accompanied by increase in the number of lymphocyte β -adrenergic receptors. Patients with orthostatic hypotension, who show low concentrations of circulating catecholamines and enhanced responses to noradrenaline and related drugs have increased number of adrenergic recep-

tors than normal subjects.

MECHANISM OF ACTION OF A DRUG

Many times the terms 'action' and 'effects' of a drug are being used as synonyms. However, it is useful to term the initial consequences of drug-cell interaction as 'action' of the drug; the remaining events that follow are called 'drug effects'.

A drug may act:

- (i) Extracellularly e.g. osmotic diuretics, and plasma expanders.
- (ii) On the cell surface : e.g. digitalis, penicillin, and catecholamines.
- (iii) Inside the cell : e.g. antimalignancy compounds, and steroid hormones.

Types of drug action : Drugs may produce their effects :

(a) by stimulation, (b) by depression, (c) by irritation, or may act (d) as replacement, (e) as anti-infective agents and (f) by modification of the immune status.

It must be emphasized that a drug produces only a quantitative and not a qualitative change in the function of the target organ.

Stimulation : Increase in the activity of specialized cells is called stimulation. Excessive stimulation produces changes in the protoplasm of the cell which may ultimately lead to depression. A drug may specifically stimulate certain portions of a particular system and depress others e.g. morphine stimulates the vagus and the oculomotor nuclei, and the chemoreceptor trigger zone but depresses the vomiting and the cough centres.

Depression : Decrease in the activity of specialized cells is called depression. Quinidine depresses the myocardium while barbiturates depress the central nervous system.

Irritation : The term irritation indicates that a drug produces effects on the growth, nutrition and morphology of living tissues. Irritation is thus a phenomenon not restricted to specialized cells but can occur in all the body tissues. Irritation produces changes in the cellular structure and is

capable of producing inflammation, corrosion and necrosis of cells. The cellular changes produced by irritation are :

(i) Precipitation of proteins, also called *astringent effect*. If the irritant, however, dissolves the precipitated proteins, the tissue damage is more extensive due to deeper penetration of the irritant. This effect is called *corrosive effect*. Many concentrated acids and alkalis exert a corrosive effect.

(ii) Dehydration.

(iii) Action on cellular enzymes, usually inhibition.

(iv) Damage to the cell wall or the nucleus (cytotoxic action).

Heavy metals like mercury and silver are irritants. Mild irritation may have therapeutic utility e.g. senna and cascara which stimulate the mucosal cells of the gastrointestinal tract are used to produce purgation; mercuric oxide in the form of eye ointment is applied to stimulate healing in blepharitis.

When an irritant agent is applied locally to the skin to relieve deep seated pain, it is referred to as *counterirritant*. Volatile oils like turpentine oil are often used in this fashion. The counterirritant is applied to the skin situated over the organ responsible for pain. It stimulates the sensory nerve endings in the skin and the afferent impulses are relayed in the cerebrospinal axis to efferent vasomotor fibres supplying the internal organ. Thus, the increased circulation to the skin has its counterpart in the deep integumental structures and viscera innervated from the same segmental level of the central nervous system. In addition, the sensory impulses emanating from the skin may interfere with the transmission of pain impulses coming from the viscera and may even produce their partial or complete exclusion by occupying the final common sensory pathway. The vasodilatation and blockade of pain impulses may explain the relief of deep seated pain.

Replacement: Drugs may be used as replacement when the production of endogenous substances is reduced. Replacement finds an impor-

tant application in the treatment of hormonal deficiencies, e.g. insulin in diabetes mellitus, thyroxine in myxoedema, and hydrocortisone in the treatment of Addison's disease.

As anti-infective agents : Drugs are used for prevention, arrest and eradication of infections; they act specifically on the causative organisms e.g. antibiotics.

Modification of immune status: Vaccines, sera and certain other agents (terramisole and corticosteroids) act by altering (enhancing or depressing) the immune status. (See Chapter 71).

The activity of a drug depends upon the concentration achieved by it in the body fluids and the tissues. Drug concentration in tissues and body fluids is influenced by :

(a) Absorption of the drug after oral or parenteral administration.

(b) Biotransformation.

(c) Excretion.

(d) Tissue affinity e.g. ultra short-acting barbiturates are mainly concentrated in the central nervous system.

(e) Condition of the body or the *milieu interior* e.g. iron is absorbed much more rapidly in individuals suffering from iron deficiency anaemia, pitocin in therapeutic doses contracts the human uterus only at full term, penicillin fails to eradicate infection in the presence of agranulocytosis.

Drugs which are toxic to a wide variety of cells are called 'protoplasmic poisons'. They act indiscriminately to produce irritation of all the cells.

A drug may act by virtue of its:

(I) Physical properties:

(a) **Colour :** A pleasant colour may exert a psychological effect e.g. tincture of cardamom.

(b) **Physical mass :** Compounds like agar and psyllium seeds absorb water when administered orally and swell in size. This initiates peristalsis and exerts a laxative action.

(c) **Smell :** Volatile oils like peppermint oil are used to mask the unpleasant smell of mixtures.

(d) **Taste :** Compounds with a bitter taste

reflexly increase the flow of hydrochloric acid in the stomach and improve the appetite. These substances are called bitters, e.g. quassia, chirata and gentian.

(e) **Osmolality** : Osmotic diuretics like mannitol, osmotic purgatives like magnesium sulfate.

(f) **Adsorption** : Kaolin and activated charcoal in the treatment of diarrhoea.

(g) **Soothing-demulcent**: Syrups as pharyngeal demulcents in the treatment of cough; calamine lotion in eczema.

(h) **Radioactivity** : ^{131}I in hyperthyroidism, ^{32}P in polycythemia vera.

(i) **Radio-opacity** : Barium sulphate as 'barium meal', organic iodine compounds for the visualisation of the urinary and biliary tracts.

(j) **Reduction in surface tension** : Cationic surfactants like cetrimide for cleaning the skin.

(k) **Electrical charge** : Heparin, a strongly acidic compound, probably exerts its anticoagulant effect by virtue of its negative charge.

(II) Chemical properties:

(a) **Acidity or alkalinity** : Dilute hydrochloric acid in the treatment of hypochlorhydria, antacids in the treatment of peptic ulcer.

(b) **Chelation** : Metals like lead and copper can be eliminated from the body with the help of substances called chelating agents. The chelating agent forms a ring structure with the molecule of the metalloid or the metal. This ring structure is non-toxic and has a high water solubility which results in its excretion in the urine. Similarly sulphhydryl (SH) groups from the compound dimercaprol (B.A.L.) combine with arsenic taken up by the cells in arsenic poisoning, and form a water-soluble complex which is eliminated in the urine.

(III) Metabolic activity:

A drug may act by modifying the function of cell membrane or may penetrate into the cell and act on the intracellular structures and various enzyme systems. Many drugs used in therapeutics act in this way.

DOSE RESPONSE RELATIONSHIP

Wide quantitative variations in drug responses can occur in different species and in the same species under different conditions. Methods have, therefore, been devised to study the phenomenon of variations in pharmacological drug response and to minimize the errors of prediction in therapeutic use of drugs.

The exact relationship between the dose and the response depends on the biological object under observation, the response measured and the drug employed. Each drug has a characteristic curve for a specified set of conditions, but in general, dose response curve conforms to the S-shaped or sigmoid type, or to segments of the sigmoid.

The magnitude of the drug effect is a function of the dose administered. Two basic types of dose-effect relationship have been observed. These are:

(a) Graded or quantitative dose-effect relationship, and (b) Quantal or all or none dose-effect relationship.

(a) **Graded or quantitative dose-effect relationship**: This type of relationship relates the size of the response in a single biological unit to the dose of the drug. As the dose administered to a single subject or discrete organ or tissue is increased, the pharmacological response also increases in a gradual fashion provided the dose has exceeded some critical level called the threshold dose (Fig. 1.11). The graded dose-response relation is partially a reflection of the extent of occupancy of the receptor by the drug. Since an entire dose response relationship is determined from one animal, the curve cannot tell us about the degree of biological variation inherent in a population of such animals.

The degree of effect produced by increasing doses of a drug eventually reaches a steady level. This phenomenon is termed as the '*ceiling effect*', and the dose with which it is obtained is the '*ceiling dose*'. If the dose of a drug exceeds the ceiling dose, there is no further increase in the

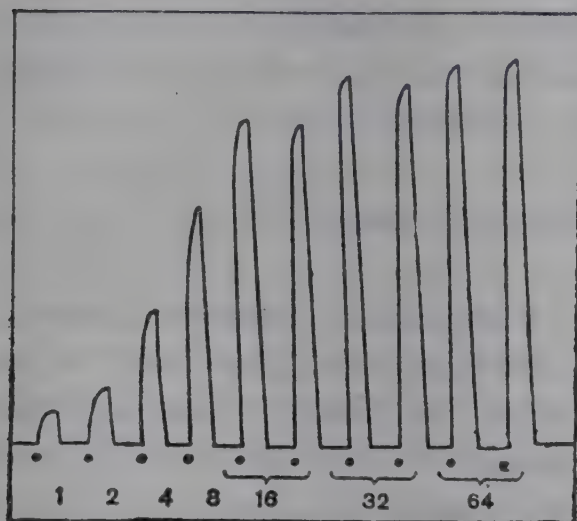


Fig. 1.11 : Effect of graded doses of histamine on isolated guinea-pig ileum.

therapeutic effect. In fact, such a dose may provoke different and possibly undesirable responses. The ceiling dose enables us to compare the therapeutic efficacy of various pharmacologically active compounds.

Although the graded dose response curve is usually sigmoid in shape, the graph plotted with drug response against the logarithm of the drug dose is almost a straight line. This '*log dose response curve*' (Fig. 1.12) is particularly useful for the comparison of the activity of various compounds, e.g. in bioassays.

(b) Quantal or all or none dose-effect relationship : In contrast to graded effects, the quantal

effects are all or none responses. The quantal curve shows the frequency with which any dose of a drug evokes a stated, fixed (all or none) pharmacological response in a subject population. It is, therefore, essentially a curve describing the probability distribution of minimum doses that produce a given effect in a population of biological objects. Each animal is categorized as responding or non-responding, according to the prior decided criterion of response. In case of lethal toxicity tests, each animal is classified as dead or alive at a specified time after the drug treatment. Obviously, some animals in a population being sensitive will respond to smaller doses of a drug while some will be resistant and need very large doses. Usually, the sensitivity of animals to different doses of a drug is distributed normally with respect to the logarithm of the dose. Thus, for a given drug, if log dose is plotted on the horizontal axis and the per cent responding (dead) to the various dose levels is plotted on the vertical axis a Gaussian (normal) distribution is obtained as shown in Fig. 1.13. The curve represents the distribution of sensitivity of a group of animals to the given drug. In this figure about 10 per cent of the animals in a given population are killed at a dose level of log dose '0', while another 10 per cent

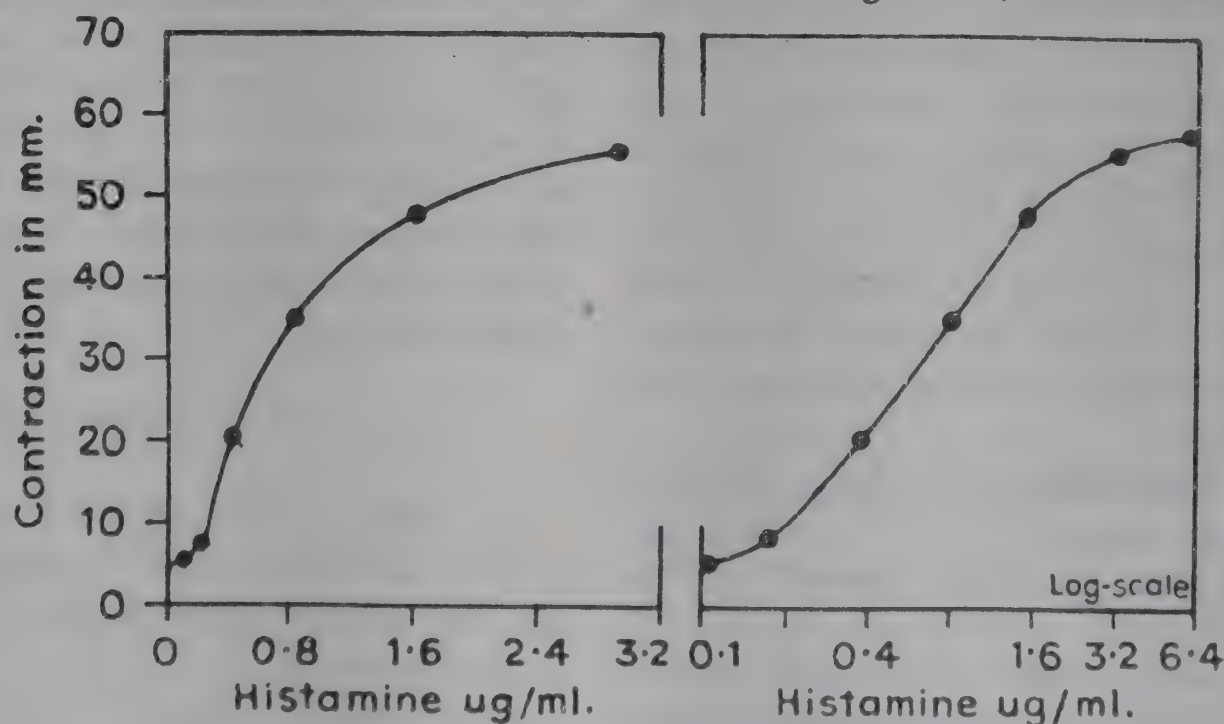


Fig. 1.12 : (a) Dose-response relationship curve from the data in Fig. 1.11.

Fig. 1.12 : (b) Same dose-response relationship plotted on logarithmic scale.

are not killed until the dose is increased to log dose '2'. Majority of the animals, however, are killed at doses between '0.5' and '1.5' on the log scale. The same data when plotted as the cumulative number of animals that responded against log dose, would give the cumulative frequency distribution - an S-shaped curve. For a given dose of a drug, a cumulative curve would give the per cent of animals responding to that dose and to all lower doses.

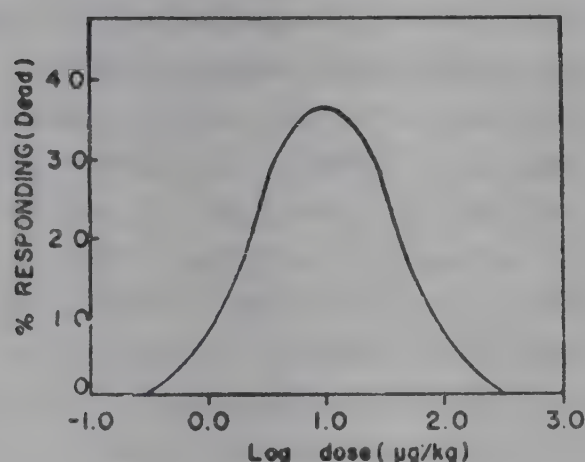


Fig. 1.13 : Quantal dose response curve

The Gaussian or normal distribution of the minimum effective dose values would suggest that the observed variation is due to random variation in the responsiveness of the animals. The quantal dose response curve, however, is not always exactly symmetrical or bell-shaped but may show 'skewing' or 'truncation'. This shows that besides random variation, other non-random but inter-coupled events like other actions of the drug, experimental limitations and genetic variations in the population influence the quantal dose response curve.

'The median lethal dose' or LD_{50} : This is the dose (mg/kg) which would be expected to kill one-half of an unlimited population of the same species and strain.

'The median effective dose' or ED_{50} : This is the dose (mg/kg) which produces a desired response in 50 per cent of the test population.

The therapeutic index: It is an approximate

assessment of the safety of the drug. It is expressed as the ratio of the median lethal dose to the median effective dose :

$$\text{Therapeutic Index (TI)} = \frac{LD_{50}}{ED_{50}}$$

As the drug metabolism varies from species to species, the therapeutic index would also vary in a similar fashion. Therapeutic index supplies reliable information when both the LD_{50} and ED_{50} are determined for the same strain belonging to the same species. ED_{50} can be obtained from either quantal or graded dose response curves.

The larger the therapeutic index, the safer is the drug. For safe therapeutic application of a compound, its therapeutic index must be more than one. Thus, penicillin has a very high therapeutic index while it is much smaller for the digitalis preparations.

In practice, no drug produces only a single effect but has a spectrum of effects. Further, a drug may be selective in one respect but non-selective in another. Thus, although anti-histaminics selectively block histamine actions, most of them cause significant sedation. For therapeutic purposes, selectivity of a drug effect is clearly one of its more important properties. The therapeutic index gives only a rough idea about the safety of the preparation. In fact, the margin of safety of aspirin when used for headache is far greater than its margin of safety for the relief of arthritic pain or in rheumatic fever. This is because the latter use requires larger doses. Depending upon its clinical use, a drug may thus have many therapeutic indices.

ADVERSE REACTIONS TO DRUGS

An adverse drug reaction is defined as "any response to a drug that is noxious and unintended and that occurs at doses used in man for prophylaxis, diagnosis or therapy" (W.H.O.).

Apart from allergic and idiosyncratic reactions, described later, administration of a drug may result in the development of :

(a) Side effects, (b) Untoward effects or (c) Toxic effects.

(a) **Side effects:** Side effects are in fact, pharmacological effects produced with therapeutic doses of the drug e.g. dryness of mouth with atropine. Side effects which might be troublesome in a particular condition may prove useful under other circumstances. Thus, dryness of mouth is undesirable when a person suffering from peptic ulcer is given atropine. Such a drying effect, however, proves useful when atropine is used as a preanaesthetic medication. Cytotoxic drugs such as cytophosphamide used to control cancer also impair the development of megakaryocytes and thus cause purpuric bleeding.

(b) **Untoward effects :** Untoward effects develop with therapeutic dose of a drug. They are undesirable and, if very severe, may necessitate the cessation of treatment e.g. vomiting and diarrhoea with para-amino salicylic acid, resistant staphylococcal diarrhoea following tetracycline therapy and potassium loss due to diuretic drugs.

(c) **Toxic effects :** These are seen usually when a drug is administered repeatedly and/or in large doses. Drug toxicity is usually the primary attribute of a drug and is dose dependent e.g. depression of respiration with morphine or deafness following dihydrostreptomycin.

TOXICITY STUDIES IN ANIMALS

In order to assess the safety of a drug, various toxicity studies are carried out in animals like mice, rats, guinea pigs, dogs and monkeys, under varying conditions of drug administration. The tests include:

(a) Acute toxicity tests.

(b) Chronic or long-term toxicity studies.

(c) Special tests for teratogenicity, mutagenicity, carcinogenicity and dependence liability.

(a) **Acute toxicity tests :** In these tests, a drug is tested for the effects of single doses by injecting graded doses (over a wide range) in

different groups of animals. The main object of an acute toxicity test is not only to establish a figure for the LD_{50} with precision, but also to learn something about the way in which the drug acts as a poison. Detailed observations are made of the effect of the drug upon important physiological functions such as locomotion, behaviour, respiration, and of the production of obvious symptoms like convulsions and vomiting. This is generally supplemented by autopsy and histological examination. Animals included in acute toxicity studies are usually observed for at least two weeks after dosing, or longer if positive signs persist. In general, the studies are conducted in several species one of which must be a rodent. Animals of both sexes and various age groups are subjected to such tests, particularly when the drug is intended for pediatric or geriatric use. These studies determine the LD_{50} , the ED_{50} and the therapeutic index for the drug under investigation.

When a combination of two or more drugs is to be used, additional acute toxicity data are required. Here, the LD_{50} of the combination is compared with LD_{50} of each of its components in the rodents.

(b) **Chronic toxicity studies :** These studies also are carried out in different animal species with different doses and usually last for a period of 90 days to over a year. Some workers prefer to study drug toxicity initially for a shorter period of 14 to 21 days to save time and embark on chronic toxicity studies only after data from the studies of shorter duration are obtained. The toxicity studies of shorter duration (14 to 21 days) are called '*subacute toxicity studies*'. The aims of the chronic toxicity studies are to study the following :

(i) *Observation of gross changes :* e.g. an increase or decrease in weight, loss of fur, behavioural abnormalities, eye changes and changes in the mating behaviour of the animals.

(ii) *Examination of effects of the drug on the individual tissues* like kidney, adrenals, heart, liver and the bone marrow. Various examinations such as histopathology, hematology, estimation of enzyme activities and specialized tests like

liver function tests are carried out.

(iii) *Carcinogenicity* : liability of the drug to induce malignancy.

(iv) *Teratogenicity* : ability of the drug to induce foetal malformations and/or death *in utero*.

(v) *Genetic effects* : Certain drugs are known to produce genetic abnormalities. As genes are bearers of hereditary information, abnormal genes may produce various types of overt and covert abnormalities in the subsequent generations.

(vi) *Dependence liability* : This is usually studied in higher mammals like cats, dogs and monkeys, and such studies are particularly vital for drugs modifying the functions of the central nervous system.

DRUG TOXICITY IN MAN

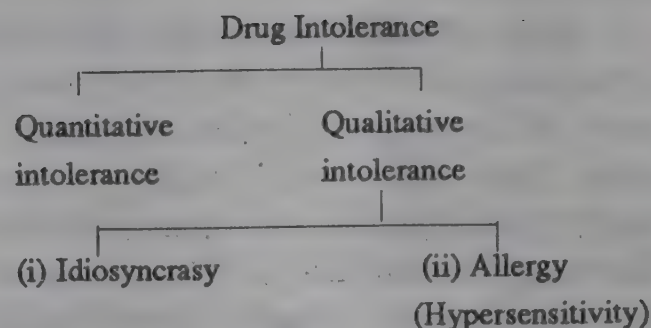
This could be (a) Local, such as irritation, necrosis, thrombophlebitis and (b) Systemic.

Serious systemic drug toxicity may result from overdose. It is usually an exaggeration of its pharmacological actions and is predictable e.g. hypotension following antihypertensive drugs and hypoglycemia following insulin. Various deleterious systemic effects produced by drugs are :

1. **Drug Intolerance** : There is considerable confusion about the term intolerance, which does not really convey a precise pharmacological meaning. Many use it to denote 'a quantitative deviation from the anticipated response to a given dose of a drug'. However, one could properly describe such normal or even hyper-responses in certain individuals to a very small dose of a drug as 'hypersensitive' responses. Unfortunately, the term 'hypersensitivity' reaction is often used to describe the 'allergic' reaction which is confusing. The literal meaning of the word 'intolerance' implies 'failure to tolerate' and should be adhered to while describing abnormal reactions to drugs. The ambiguous term 'hypersensitivity' should be avoided since with different people it carries different meanings.

Thus, drug intolerance is inability of the individual to tolerate a drug. It may be further clas-

sified as :



(a) **Quantitative intolerance** : Some individuals show a hyper-response to the therapeutic or even smaller doses of the drug, e.g. vomiting with a single dose of salicylates or giddiness with one injection of streptomycin. In fact, these are the individuals at the lower end of the frequency distribution in a quantal log-dose response curve and may be considered as hyper-reactors. (See Fig. 1.13).

(b) **Qualitative intolerance** : The symptoms and signs seen in qualitative intolerance are totally different from those seen after administration of the toxic dose of the drug.

(i) **Idiosyncrasy** : This is qualitative intolerance due to other than immune mechanisms. In certain instances, the mechanism is now known e.g. abnormal reactions to the drug are precipitated sometimes because of genetically determined total absence or reduced activity of some enzyme(s) in the body of the recipient, e.g. drugs like primaquine, salicylates, sulfonamides and the nitrofurans produce haemolysis in individuals whose red blood cells lack the enzyme glucose 6-phosphate dehydrogenase; the short-acting skeletal muscle relaxant succinylcholine may produce respiratory paralysis and prolonged apnea in individuals whose plasma contain an atypical pseudocholinesterase enzyme. The ability of this enzyme to degrade succinylcholine is poor as compared to that of the normal serum pseudocholinesterase. In many cases, the cause of the idiosyncratic phenomena is not known e.g. cholestatic jaundice following chlorpromazine and chloramphenicol induced aplastic anemia. In

general, all unusual idiosyncratic reactions to drugs should be considered genetically determined until proved otherwise.

(ii) **Allergic reactions (hypersensitivity):** Most of the drugs and sera used in therapeutics are capable of causing 'allergic' or 'hypersensitivity' reactions. These reactions may be mild or may be very severe like anaphylaxis and have immunological basis. They occur in individuals who have been sensitized following the prior administration of the same drug. To understand how drugs cause such reactions it is necessary to know some basic immunological concepts.

Antibodies are molecules found in the plasma, body secretions, and on cell surfaces produced in response usually to the presence of foreign substances called '*antigens*' or '*immunogens*'. When an antigen enters the body two types of immunological reactions may occur:

(1) The synthesis and release of a free antibody into the blood and other body fluids (*Humoral Antibody*). It is found in the beta and gamma globulin fractions of the plasma proteins and acts by directly combining with and neutralising the immunogen (e.g. a bacterial toxin) or by coating the bacteria to enhance their phagocytosis (opsonization).

(2) Production of 'sensitized' lymphocytes with antigen receptors on their surface. These cells are effectors of cell mediated immunity (CMI) involved in such reactions as delayed hypersensitivity responses.

In both these immunoresponses, lymphocytes play a central role (Fig. 1.14). The lymphocytes involved belong to two different, small-lymphocyte populations :

(a) *T-lymphocytes*, so designated because they are processed by or in some way dependent on the thymus. These lymphocytes are responsible for *cell mediated immunity*. They do not themselves secrete antibody but may help the antigenic stimulation of B-lymphocytes to be more effective.

(b) *B-lymphocytes*, so named because of their relation to the Bursa of Fabricius, a lymphoid

organ similar to thymus, found in chicken. B-lymphocytes are concerned with the synthesis of *circulating humoral antibody*. In humans, B-lymphocytes develop directly from lymphoid stem cells in the haemopoietic tissue of foetal liver. In adults this function is transferred to the bone marrow.

Both lymphocyte populations, when stimulated by an appropriate antigen, proliferate and undergo morphological changes. (Fig. 1.14). Antibodies are globulins, also designated as immunoglobulins or Ig, and migrate electrophoretically as gamma and beta globulins. Depending upon their characteristics, five major groups of antibodies have been defined in man. They are IgG, IgA, IgM, IgD and IgE. The important properties of various immunoglobulins are given in Table 1.1. Apart from their role in body's defence mechanism, certain antibodies (IgE) also have other properties such as fixing to basophils and mast cells (*Homocytotropic* or *reaginic antibodies*), which can cause unpleasant and sometimes dangerous reactions. The ability to recognize and respond to one particular antigen rather than to another (specificity) and the ability to recognize and respond more vigorously to an antigen encountered for the second or subsequent time (memory), are the two important features of the immunological responses involving antibodies.

Generally, proteins with molecular weight of over 5,000, when administered parenterally, readily stimulate the production of antibodies. Peptides of molecular weight less than 5,000 are less immunogenic. Nonprotein compounds such as drugs can become immunogenic after chemical coupling to a carrier protein and produce antibodies that can react with the drug which thus behaves as *haptens*. A hapten is a substance which is antigenic in the sense that it reacts with an antibody but itself is incapable of stimulating antibody production unless combined with a carrier protein.

When an individual has been sensitized to an antigen (allergen), further contact with that anti-

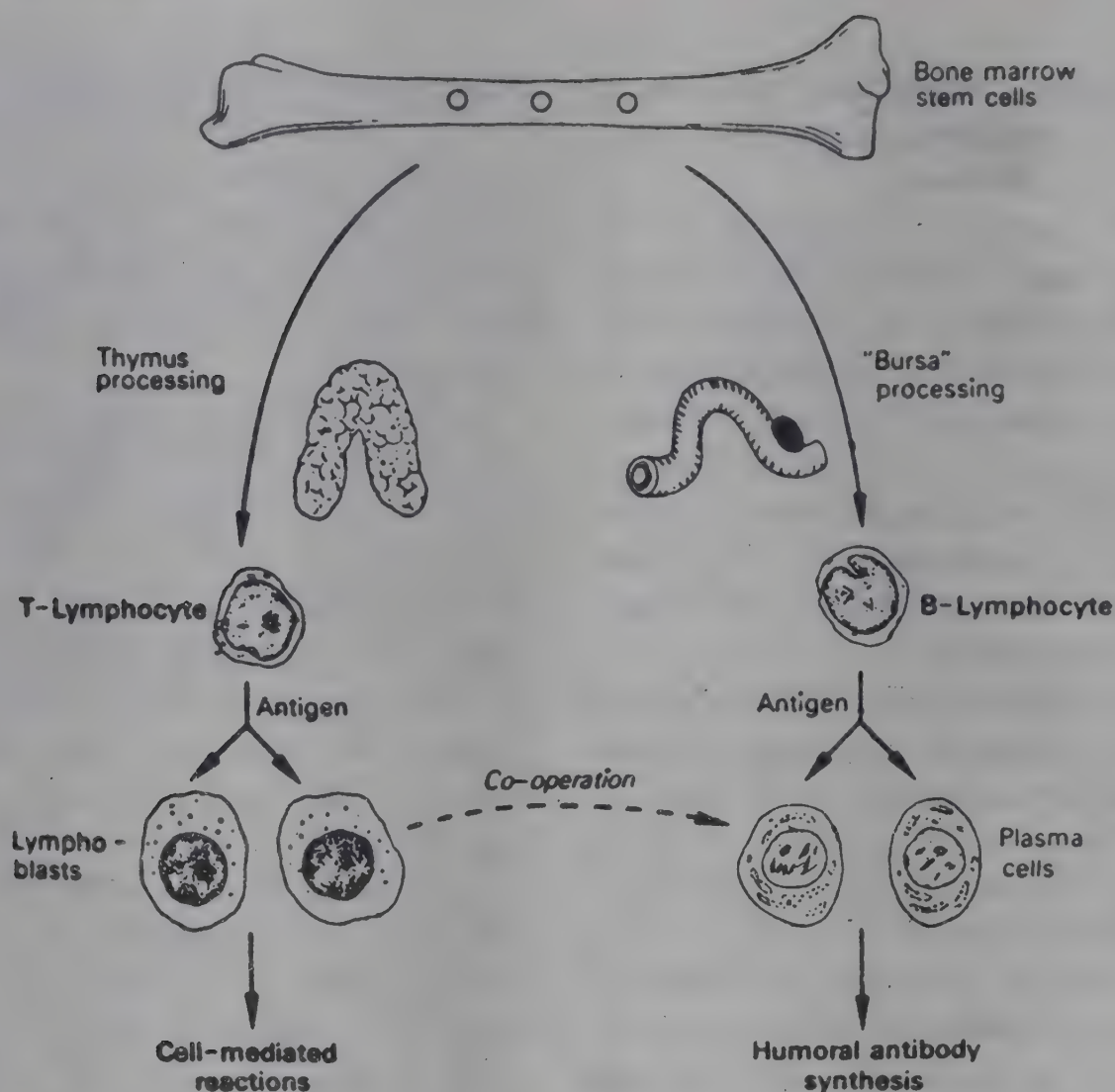


Fig. 1.14 : Processing of bone marrow cells by thymus and gut associated central lymphoid tissue to become immunocompetent T- and B-lymphocytes respectively. Proliferation and transformation to cells of the lymphoblast and plasma cell series occurs on antigenic stimulation. (From 'Essential Immunology' by Ivan Roitt. Courtesy of Blackwell Scientific Publications and Author).

gen can sometimes lead to tissue-damaging reactions called 'hypersensitivity' or 'allergic' reactions. These are :

(1) **IgE mediated 'allergic reactions and anaphylaxis (Type I reactions) :** A single injection of egg albumin into a guinea pig has no obvious effect. However, antibodies are formed to this protein and the animal is sensitized. A repeat injection of egg albumin in such an animal causes a violent reaction called anaphylaxis. The animal gets asphyxiated from bronchospasm, the blood pressure falls due to vasodilatation and death occurs within a few minutes. A similar systemic reaction can occur in a sensitized human subject following a repeat injection of drugs like penicillin. This is the phenomenon of systemic anaphylaxis. The reaction can also be demonstrated in the isolated lung or uterus preparation

obtained from a guinea pig previously sensitized to egg albumin. Addition of egg albumin to such a preparation causes intense bronchoconstriction or a maximal uterine contraction.

Systemic changes in anaphylaxis resemble those produced following an injection of histamine. The antigen reacts with a specific class of antibody, reaginic antibodies (IgE), bound to the surface of mast cells and basophils. Interaction of antigen with these antibodies increases the cell membrane permeability with influx of calcium ions into the cells. This causes degranulation of mast cells and basophils with massive liberation of histamine and other mediators of immediate hyper-response, leading to anaphylaxis in man.

In certain animal species, another mediator 5-hydroxytryptamine (serotonin) is also released. Other highly active, preformed mediators re-

leased from the basophil-mast cell granules include platelet activating factor (PAF), heparin, certain enzymes and chemotactic factors for both polymorphs and eosinophils. Further, triggering of the basophil-mast cells also causes the activation of cell membrane phospholipase A_2 which leads to release and metabolism of arachidonic acid. This results in the production of prostaglandins and thromboxane via the cyclooxygenase pathway and of various leukotrienes through the lipoxygenase pathway. Slow reacting substance (SRS-A), discovered earlier, is in fact a mixture of leukotrienes LC_4 , LD_4 and LE_4 (See Chapter 21). All these mediators play an important role in the genesis of anaphylaxis. It must be noted, however, that under more controlled conditions, mast cell triggering forms a vital part of the defensive acute inflammatory reaction.

Different species vary considerably in their response. Thus, anaphylaxis can be readily in-

duced in the guinea pig, much less easily in the rabbit and the least in the rat.

Anaphylactic shock in a guinea pig produces death as a result of severe bronchospasm and acute pulmonary edema leading to immediate ventilatory failure. In dog, rabbit and cat, death is caused by right-sided cardiac failure related to acute pulmonary hypertension, largely due to selective constriction of the pulmonary arterioles, and is accompanied by pooling of blood in the splanchnic area. In humans, death is usually due to laryngeal edema, a unique feature in man, to severe bronchospasm leading to asphyxia, or to circulatory collapse. As the peripheral arterial resistance is found to increase markedly owing to compensatory sympathetic overactivity, the circulatory collapse observed is attributed to a marked decline in the cardiac output. This occurs mainly as a result of reduction in the circulatory blood volume secondary to loss of fluid from the intravascular compartment and may partly be due

Table 1.1 : Biological properties of major Immunoglobulin classes in the human

	IgG	IgA	IgM	IgD	IgE
Major Characteristics	Most abundant Ig of internal body fluids particularly extravascular where it combats micro-organisms and their toxins; synthesized in secondary antibody response	Major Ig in seromucous secretions where it defends external body surfaces	Very effective agglutinator, produced early in immune response - effective first line defence vs. bacteraemia; rheumatoid factor.	Present on B lymphocyte surface	Protection of external body surfaces; recruits antibacterial agents; raised in parasitic infections; responsible for symptoms of atopic allergy and anaphylaxis
Complement fixation					
Classical	++	---	+++	---	---
Alternative	+	+	---	+	+
Cross placenta	+	---	---	---	---
Fix to mast cells (in homologous skin) and basophils	---	---	---	---	+
Cytophilic binding to macrophages and polymorphs	±	---	---	---	---
Average adult serum level (mg/dl)(± 300)	1250	210 (± 50)	125 (± 50)	4	0.03
Half life (days)	23.0	5.8	5.1	2.8	2.5

Modified from 'Essential Immunology' by Ivan Roitt; Publishers; Blackwell Scientific Publications.
By courtesy of the Publishers and Author.

to myocardial injury. The ECG of patients suffering from anaphylactic shock shows acute S-T and T wave changes.

As compared to systemic anaphylaxis, *local anaphylactic reactions* (*atopic allergy*) to extrinsic antigens (allergens) such as pollen, animal danders, mites in house dust and absorbed food-stuffs occur more frequently in man. Combination of the allergen with cell bound IgE antibody in the bronchial tree, the nasal mucosa or the skin releases mediators of anaphylaxis giving rise to localized reactions such as, asthma, rhinitis or urticaria. The offending antigen can be identified by intradermal prick test, giving rise to immediate wheal and erythema reactions. There is a strong familial tendency. The symptoms of atopic allergy are to a certain extent controllable with antihistaminic drugs and other mediator antagonists (see Chapter 20). Courses of antigen injection may desensitize by forming blocking IgG or IgA antibodies, or by turning off IgE production.

(2) **Cytotoxic type reaction (Type II)** : In this case, the antibodies bind to an antigen present on the cell surface and promote phagocytosis of the cell or cell destruction by lysis. Such cells bearing IgG on their surface may also be killed by polymorphs and macrophages or by non-adherent lymphoid killer cells (K cells) through an extracellular mechanism. Transfusion reactions, anti-D antibodies in Rhesus incompatibility and antibodies to kidney glomerular basement membrane are examples of this type of reaction. Drugs can form an antigenic complex with the surface of a formed element of the blood and can evoke the production of humoral antibodies which act as cytotoxic for the cell-drug complex, leading to hemolysis, agranulocytosis or thrombocytopenia.

(3) **Immune Complex mediated reaction (Type III)** : The union of soluble antigen with humoral antibody *in vivo* can form immune complexes which may ultimately cause histamine release, activation of kinin system and aggregation of platelets with formation of microthrombi and further release of vasoactive amines. The attracted polymorphs release tissue-damaging

enzymes on contact with the complex. In case of high levels of circulating antibodies, the antigen is precipitated near the site of entry into the body. The reaction in the skin is characterised by erythema, edema and cellular infiltration, maximal at 3 - 8 hours (Arthus reaction). When the antigen is relatively in excess, soluble complexes are formed, circulate in the body and deposit at certain preferred sites such as the skin, the joints, the renal glomeruli and the choroid plexus. This type of reaction is observed in serum sickness following the injection of large quantities of foreign protein such as horse serum, and in glomerulonephritis associated with systemic lupus erythematosus or infections. Intrapulmonary Arthus type reactions to exogenous, inhaled antigens appear to be responsible for many hypersensitivity disorders such as farmer's lung; such reactions are often provoked by the local release of antigens from infective organisms within the body. Thus, chemotherapy may cause an abrupt release of microbial antigens, producing dramatic immune-complex mediated reactions such as erythema nodosum leprosum in lepromatous leprosy patients, and the Jarisch-Herxheimer reaction in syphilitics treated with penicillin.

(4) **Cell mediated reaction (Delayed hypersensitivity) (Type IV)** : In this case, T-lymphocytes carrying a specific receptor on their surface are stimulated by contact with the antigen to release certain active factors. This form of allergic phenomenon is observed in contact dermatitis and in diseases caused by chemicals, dusts, mycobacteria, chlamydia, fungi and helminths, and in the rejection of transplanted tissue. Inflammatory reactions initiated by mononuclear lymphocytes and not by antibody alone are called *delayed hypersensitivity reactions*. The word *delayed* is used to contrast the secondary cellular response which appears at 48-72 hours after the antigen exposure with the *immediate* hypersensitivity response seen within 12 hours of the antigen challenge, initiated by basophil mediated reactions (Type I) and by preformed antibodies (Types II and III). The dermal route of antigen in-

oculation tends to favour the development of a T-cell response. A typical delayed hypersensitivity response is observed in the Mantoux reaction following the intradermal tuberculin injection, wherein an indurated and erythematous reaction occurs within 48 hours. It is characterised histologically by infiltration with mononuclear phagocytes and lymphocytes (granulomatous infiltration). Delayed type of reactions are often observed with drugs that are capable of binding to body constituents and form new antigens e.g. sulphonamides, penicillin, neomycin and metals like nickel and following insect bites. The phenomenon is also observed following contact with certain plants or food in sensitized individuals.

The mechanism of delayed hypersensitivity is not known but different types of immune reactions can produce delayed hypersensitivity. Unlike other forms of hypersensitivity, it cannot be transferred from one animal to another by serum but can be transferred by T lymphocytes. T lymphocytes necessary for producing delayed hypersensitivity (T_D cells) are cells which have become sensitive to particulate antigens by a previous encounter. Other cell types are also recruited to the site of the reaction.

(5) **Stimulatory reaction:** In this immunological phenomenon, the noncomplement fixing humoral antibodies directed against certain cell surface components may actually stimulate rather than destroy the cell. Thus, a long-acting thyroid stimulator (LATS) is an autoantibody, probably directed against an antigen on thyroid follicular surface, which stimulates the cell and produces similar actions as pituitary TSH.

Desensitisation : This term is used to describe two different processes. In one case the second dose of antigen fails to evoke any response in a sensitized preparation. This may be due to exhaustion of antibody or of an essential enzyme system activated by the antigen-antibody reaction. The second type of desensitization is the one which is carried out in therapeutic practice. In this case, a course of graded injections of an antigen is given to a hypersensitive patient in order to render him less responsive to the antigen. The exact

mechanism how this happens is not known, but it is believed to be due to formation of blocking antibodies. Thus, blocking antibodies combine preferentially with antigen and make it inactive.

Among the various types of allergic reactions, anaphylactic shock is a serious medical emergency and needs immediate and energetic treatment. (See Chapter 20)

(II) **Haemopoietic toxicity :** Haemopoietic toxicity ranges from anaemia to various blood dyscrasias like leucopenia, granulocytopenia, agranulocytosis, aplastic anaemia and thrombocytopenia. The reduction in clotting factors may lead to severe haemorrhages. (See Chapter 32).

(III) **Hepatotoxicity :** Drugs can cause liver toxicity (a) by *direct action*, either themselves or more commonly through their metabolites (e.g. carbon tetrachloride and isoniazid) and (b) by *immunological reaction*, which renders a constituent of the liver antigenic.

The direct or metabolite induced hepatotoxicity is predictable, dose related and can be demonstrated in animal models; other organs such as kidney may also be affected. It may manifest as asymptomatic hepatomegaly, acute hepatic necrosis (tetracycline, halothane), altered hepatic metabolism (chloramphenicol) or as altered bilirubin metabolism, interfering with uptake of bilirubin (sulfonamide, salicylates). Rarely, acute intermittent porphyria may occur.

As against this, hepatotoxic reactions with immunological basis are unpredictable, not dose related and have no animal models. Usually, they are selective and restricted to the liver, although other general allergic manifestations may be present. Such toxicity may cause non-specific hepatitis resembling viral hepatitis (isoniazid, pyrazinamide, indomethacin), cholestasis interfering with biliary secretion causing hyperbilirubinemia (certain anabolic steroids) or cholestatic hepatitis (chlorpromazine, chlorpropamide).

In case of some drugs such as methyldopa, chlorpromazine and isoniazid both the mechanisms can operate.

(IV) **Nephrotoxicity** : Some drugs can cause albuminuria, hematuria and even tubular necrosis. The therapeutically ineffective acetylated form of sulfonamides may get precipitated in the urinary tract, especially when the urine is acidic and may produce renal calculi. (See Chapters 9 and 35).

(V) **Behavioural toxicity** : Compounds like reserpine may produce suicidal tendencies; amphetamine may cause disorientation, confusion and inability to concentrate; the glucocorticoids may produce euphoria, restlessness and psychosis. For behavioral teratogenicity, see Chapter 72.

(VI) **Unmasking and exacerbation of disease** : Drugs can exacerbate an already existing disease or unmask a latent condition, e.g. glucocorticoids unmask latent diabetes and may exacerbate an existing peptic ulcer. Isonicotinic acid hydrazide may unmask latent epilepsy.

(VII) **Production of a disease (Iatrogenic disease)** : Sometimes, drugs themselves may produce certain pathological syndromes. Such diseases produced as a result of therapeutic measures are known as '*iatrogenic diseases*', the Greek word '*iatros*' meaning "physician". Thus, chlorpromazine and reserpine may cause parkinsonism while glucocorticoids can precipitate hypertension and congestive cardiac failure. Glucocorticoids, aspirin and indomethacin may precipitate perforation of peptic ulcer; and vigorous oxygen therapy in a premature infant is known to result in the development of retrolental fibroplasia.

(VIII) **Electrolyte disturbances** : Diuretics like chlorothiazide and furosemide produce loss of sodium as well as potassium in the urine and may produce hypokalemia. Corticosteroids, particularly cortisone and hydrocortisone, produce sodium retention and edema.

(IX) **Endocrine disturbances** : Chlorpromazine, on prolonged administration, may produce menstrual irregularities and can even cause galactorrhoea and amenorrhoea. Oral contraceptives may arrest lactation in nursing mothers. Glucocorticoids like cortisone and hydrocorti-

sone usually depress the synthesis of ACTH and the endogenous corticoid hormones. Abrupt withdrawal of these compounds may, therefore, precipitate acute hypocorticism or Addisonian crisis while vigorous therapy may cause Cushing's syndrome. Cushing's-like syndrome is seen in chronic alcoholics, and a variety of endocrine disturbances are caused by phenytoin.

(X) **Skin toxicity** : The skin is a common target organ for various allergic reactions. In addition, metalloids like arsenic and heavy metals like mercury are secreted in the sweat in small amounts and can thus produce skin rash.

(XI) **Toxicity due to drug interaction** : This can occur when two or more drugs are administered simultaneously to a patient. (See Chapter 2).

(XII) **Carcinogenesis** : Estrogens exacerbate mammary carcinoma in menstruating females but they may reduce the size of the growth and the extent of metastases if administered to post-menopausal patients. Increased risk of developing endometrial cancer has been reported in women receiving prolonged estrogen therapy without concomitant progesterone.

(XIII) **Teratogenicity** : The word is derived from the Greek word '*teros*' which means 'monster'. The sedative 'thalidomide', prescribed to pregnant women for giving relief from morning sickness, was found to produce various types of developmental anomalies in the newborns. The commonest anomalies were 'amelia' or total absence of limbs, and 'phocomelia' or absence of one or more limbs. (Fig. 1.15 see art plate). The thalidomide tragedy has prompted various nations to impose strict teratogenicity tests on new drugs before their introduction into therapeutics. However, it may be pointed out that although the list of drugs showing teratogenicity in animals is formidable, clinically only a few drugs have been shown to produce such an effect. (For details, see Chapter 72.)

(XIV) **Drug dependence** : Certain drugs, when used repeatedly, may make the individual psychologically and physiologically dependent on them. This phenomenon of *drug dependence* is

discussed later.

(XV) **Adverse reactions precipitated by abrupt drug withdrawal** : Abrupt cessation of administration of several groups of drugs after prolonged use is known to cause adverse reactions. The underlying disease may undergo exacerbation; a typical 'withdrawal syndrome' may occur; or symptoms may occur as a result of adaptive changes in the body (pituitary suppression by corticosteroids). The withdrawal syndrome after cessation of opioids is discussed in Chapter 8. A similar withdrawal syndrome has been described after abrupt cessation of prolonged administration of hypnotic drugs such as barbiturates and benzodiazepines; it is particularly likely to occur after cessation of drugs with a short half life e.g. amylobarbitone, butabarbitalone, triazolam and lorazepam. Sudden cessation of antidepressant drugs can lead to a recurrence of depression. The effects of sudden cessation of anticonvulsants (Chapter 7), beta-adrenergic blockers (Chapters 14 and 27), clonidine (Chapter 26) and corticosteroids (Chapter 61) are discussed elsewhere in this book. With such drugs, the cessation of therapy must be gradual, with small decrements and under close medical supervision. Sometimes, substituting a drug with a longer half life (e.g. methadone in patients taking an opioid, phenobarbitone in patients taking a barbiturate, and diazepam or flurazepam in patients taking a benzodiazepine) is helpful in bringing about a successful and uneventful withdrawal of the drug under consideration.

Treatment of acute drug poisoning:
The principles of treatment are :

(i) *Removal of the poison* : In a conscious patient vomiting can be induced by tickling the back of the pharynx. Ipecac syrup 15 ml. followed by 200 ml. of water is useful in inducing vomiting in many cases including infants. Though salt and water can induce vomiting it may cause hypernatremia. In the hospital, the ingested poison can be removed by gastric aspiration and lavage using a wide bore tube with patient tilted head down and on his left side. Absorption of a poison from the gastrointestinal tract can be reduced in certain

cases by using the *universal antidote*. The composition of the universal antidote is 2 parts of powdered charcoal with 1 part of tannic acid and 1 part of magnesium oxide. The universal antidote is particularly useful for reducing the absorption of alkaloids from the gastrointestinal tract. A home made substitute for the universal antidote is two parts of burnt toast, one part of strong tea and one part of milk of magnesia.

Elimination of the poison can be enhanced by:

(a) increasing the urine output by means of diuretics like mannitol, furosemide.

(b) by adjusting the reaction of urine; acidic drugs are excreted faster in an alkaline urine and alkaline drugs in an acidic urine and

(c) by dialysis.

(ii) *Administration of specific antidote* e.g. naloxone for acute morphine poisoning, dimercaprol for acute arsenic poisoning and E.D.T.A. for acute lead poisoning.

(iii) *Supportive treatment* such as maintenance of a patent airway, assisted mechanical ventilation, maintenance of blood pressure by vasopressor agents, nutrition by intravenous glucose saline and prevention of secondary infection.

Self-medication is often an important cause of drug poisoning. This is particularly true of a commonly used and 'available over the counter' drugs like fever and pain remedies and vitamin D preparations.

FACTORS MODIFYING THE EFFECTS OF A DRUG

Individuals differ both in the degree and the character of the response that a drug may elicit and, therefore, the optimum dose of a drug which produces the desired therapeutic effect varies from person to person. The doses of official preparation of drugs are, therefore, always expressed in the form of a range which gives the therapeutic effect in majority of subjects. The dose range is usually based on the average requirements of an adult patient and may not be applicable under all circumstances. The important factors which influence the effect of a drug are :

I. Body weight : The average dose is mentioned either in terms of mg. per kg. body weight or as the total single dose for an adult weighing between 50-100 kg. However, dose expressed in this fashion may not apply in cases of excessively obese individuals or those suffering from edema, dehydration or emaciation. Nutritional factors can sometimes alter drug metabolizing capacity and this should be kept in mind in cachectic and malnourished patients.

II. Age : The pharmacokinetics of many drugs changes with age. Thus gastric emptying is prolonged and the gastric pH fluctuates in neonates and infants. Further, the liver capacity to metabolize drugs is low, renal function is less developed and the proportion of body water is higher in the new born and the neonates. Hence, children may not react to all drugs in the same fashion as young adults. They are more sensitive to the depressants of the central nervous system while they tolerate relatively larger amounts of belladonna, ethanol and digitalis on body weight basis than adults. The metabolic clearance of drugs such as chloramphenicol, barbiturates, pethidine, salicylates, sulfonamides, diazepam and aminoglycoside antibiotics is less in infants than in adults. With a few exceptions, drugs are more active and more toxic in the newborn than in older animals. The doses of sera like antidiphtheria serum (ADS) and antitetanus serum (ATS), however, are not modified by age.

The pediatric doses are expressed in terms of body weight (mg/Kg per dose or daily) or in terms of body surface area (mg/M² per dose or daily). The body surface area is calculated from the height and weight of the child. It should be emphasized that it is better to rely on a handy reference book than on one's memory during pediatric prescribing.

Like children, old people also present problems in dosage adjustment and this may vary widely with different people. The metabolism of drugs may diminish in the elderly and the renal function declines with age. Further, elderly pa-

tients are apparently more sensitive to some drug effects. Central depressant drugs e.g. hypnotics, tranquillizers may produce confusional states in the old people. Plasma half lives of drugs such as phenylbutazone, diazepam, pethidine and propranolol are longer in the elderly.

Table 1.2 : Determination of Children's Doses from Adult Doses on the Basis of Body Surface Area*

Weight (kg)	Approx. surface area in square meters	Approx. percentage of adult dose **
2	0.15	9
4	0.25	14
6	0.33	19
8	0.40	23
10	0.46	27
15	0.63	36
20	0.80	46
25	0.95	55
30	1.08	62
35	1.20	70
40	1.30	75
45	1.40	81
50	1.51	87
55	1.58	91

* Based on Done, A.K. : "Drugs for Children" in Modell, W. (Ed) Drugs of Choice 1972-73. St. Louis : The C.V. Mosby Co., 1972.

** Based on average adult surface area of 1.73 sq meters.

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III. Sex : Depressants of the central nervous system like morphine and barbiturates may sometimes evoke excitement in the females. Special care should be exercised when drugs are administered during (a) menstruation, (b) pregnancy, and (c) lactation.

(a) *Menstruation* : Drugs producing pelvic congestion, e.g. drastic purgatives, should be avoided during menstruation.

(b) *Pregnancy* : Drugs which may stimulate the uterine smooth muscle are contraindicated during pregnancy. Further, many drugs admini-

stered to the mother are capable of crossing the placenta and affecting the fetus. (See Chapter 72)

(c) *Lactation* : This is discussed in Chapter 72.

IV. Diet and Environment : Medicines are usually taken after meal to reduce the risk of gastric irritation and its attendant nausea and vomiting. Food, however, can have significant effect on the pharmacokinetics of drugs. Generally, food depresses the rate and the extent of drug absorption. Drugs may be given under certain circumstances on empty stomach (i) to prevent mixing with the foodstuffs e.g. the anthelmintics, (ii) to get an immediate action e.g. drugs used against motion sickness, and (iii) to prevent drug inactivation in the gut e.g. penicillin V. Tetracyclines form insoluble chelates with aluminium, calcium and magnesium salts, which reduces their absorption. Captopril, digoxin and rifampicin are examples of drugs better absorbed on empty stomach.

The amount of barbiturate required to produce sleep during daytime is much higher than the dose required to produce sleep at night. High altitude with concomitant low barometric pressure diminishes the capacity of the body to oxidize drugs and this may precipitate drug toxicity. Polycyclic hydrocarbons present in the cigarette smoke and hydrocarbon pesticides such as D.D.T. which induce hepatic microsomal enzymes, increase the biotransformation of drugs such as theophylline. Consumption of alcohol modifies the response to many drugs. Alcohol also induces hepatic enzymes and causes rapid metabolism of certain drugs. On the other hand, hepatic injury due to alcohol can increase sensitivity to drugs.

V. Genetic factors : Explanation is now available for some of the individual variations in the response to drugs. The science of *pharmacogenetics* is concerned with the genetically mediated variations in drug responses. It should be noted that patients with hereditary metabolic disorders rarely show a disturbance in the metabolism of drugs and other foreign compounds. This

is because the microsomal enzyme system, involved in the metabolism of drugs, do not participate to a significant extent in the intermediary metabolism. The important examples of genetic variations are :

(a) *Acetylation and hydroxylation of drugs* : The rate of acetylation of INH, dapsone, hydralazine, procainamide and some sulfonamides is controlled by an autosomal recessive gene and the dosage of these drugs depends upon the acetylator status of individuals. Similarly, slow hydroxylators are liable to exaggerated responses (severe hypotension with debrisoquine and excessive beta blockade with metoprolol) and to drug toxicity (lactic acidosis with phenformin and hepatotoxicity with perhexilene). Finally, primary lung carcinoma in Nigerians is seen predominantly in fast hydroxylators, and bladder carcinoma in dye workers is more commonly seen in slow acetylators.

(b) *Plasma cholinesterase* (Pseudocholinesterase) : Some persons inherit a modified type of esterase (atypical pseudocholinesterase) that is less efficient than the normal enzyme in hydrolysing the drug succinylcholine. Such people may develop prolonged respiratory paralysis even with a therapeutic dose of succinylcholine. This is discussed in Chapter 18.

(c) *Phenytoin hydroxylation* : Certain individuals are unable to p-hydroxylate diphenylhydantoin and develop marked toxicity, during phenytoin therapy.

(d) *Glucuronide conjugation* : Many drugs and even endogenously occurring compounds like bilirubin are conjugated as glucuronides. In a hereditary disorder termed Crigler-Najjar syndrome, the conjugation of bilirubin is impaired, resulting in a severe nonhemolytic jaundice, kernicterus and cerebral disturbances. Some of these cases benefit from phenobarbitone therapy.

(e) *Erythrocyte diaphorase* : The enzyme erythrocyte NAD-diaphorase protects the erythrocytes by reducing methemoglobin to hemoglobin. Individuals with a hereditary deficiency of this enzyme are likely to develop methemo-

globinemia after administration of drugs such as acetanilid, sulfonamides and nitrites.

(f) *Glucose-6-phosphate dehydrogenase* : Primaquine and a variety of other drugs cause hemolysis in individuals with a deficiency of glucose-6-phosphate dehydrogenase. See Chapter 32.

(g) *Miscellaneous* : These include abnormal drug response in miscellaneous hereditary conditions, such as,

(i) Inherited resistance to coumarin anticoagulants.

(ii) Chinese patients tend to respond to lower doses of propranolol than do the Western patients although the metabolism of propranolol is significantly faster in the Chinese than in the white group.

About 90% of whites have in their liver a form of alcohol dehydrogenase which metabolizes alcohol *in vitro* more slowly than the corresponding liver enzyme in 90% of orientals. Genetic variations in the activity of aldehyde dehydrogenase among various ethnic groups have also been reported.

(iii) Exaggerated pupillary dilatation following local instillation of atropine or hydroxyamphetamine in patients with mongolism. A normal therapeutic dose of atropine may even prove fatal in such patients. Topical application of corticosteroids to eye may precipitate glaucoma in some patients.

(iv) Barbiturates markedly enhance the activity of the hepatic enzyme delta-aminolevulinic acid synthetase leading to a marked rise in the rate of porphobilinogen synthesis. This precipitates an acute attack of porphyria in susceptible individuals, leading to paralysis or even death.

(v) Precipitation of severe hyperpyrexia, muscle rigidity, hyperkalemic cardiac arrest and death (malignant hyperthermia, an autosomal dominant condition) by anaesthetics such as halothane, methoxyflurane and cyclopropane.

VI. Route of administration: Intravenous doses of the drugs are usually smaller than oral doses, particularly in case of drugs which are incompletely absorbed orally e.g. morphine and

digoxin. The onset of drug action is obviously much quicker with the intravenous route; this might also enhance the chances of drug toxicity.

VII. Emotional factors : The personality of the physician may influence the drug effect considerably, particularly if the drug is intended for use in a psychosomatic disorder. Inert dosage forms called placebos resemble the actual medicament in the physical properties. Placebos are known to produce therapeutic benefit in conditions like angina pectoris and bronchial asthma. The personality of the patient may also modify the drug effect. The dose of chlorpromazine required to produce tranquillization in an otherwise normal individual is 50 to 100 mg. However, the same drug has to be administered in the dose of 500 to 1000 mg. to achieve the quietening effect in some schizophrenic patients.

VIII. Metabolic disturbances : Changes in water, electrolyte balance and acid base balance, body temperature and other physiological factors may modify the effects of drugs e.g.

(a) Salicylates reduce body temperature only in the presence of pyrexia, while they have no temperature lowering effect if the body temperature is normal.

(b) The vasoconstrictor effect of noradrenaline is reduced in the presence of metabolic acidosis.

(c) The absorption of iron from the gastrointestinal tract is maximum if the individual has an iron deficiency anemia.

IX. Presence of disease: Drugs like barbiturates and chlorpromazine may produce unusually prolonged effect in cirrhotic patients. Antibiotics like streptomycin and kanamycin, excreted mainly by the kidneys may prove toxic if the kidney function is impaired. In myxedema, morphine acts for a much longer time because of the low rate of oxidation. In congestive heart failure, the clearance of lignocaine may diminish by 50%. Pulmonary and gastrointestinal disease may also alter pharmacokinetics.

X. Cumulation : If a drug is excreted slowly, its administration may build up a sufficiently high concentration in the body to produce

toxicity e.g. digitalis, emetine and heavy metals. Sometimes, a cumulative effect is desired e.g. with phenobarbitone in the treatment of epilepsy. Most often, however, it is undesirable. Apparent cumulation occurs when an insoluble substance in the form of a suspension is injected into the body. Such a preparation, however, releases the active drug slowly and does not produce toxicity e.g. long acting hormone preparations. Substances like lead can remain deposited in bones without producing toxic effects. This is called passive cumulation. It would produce the toxic manifestations as soon as it is released into the blood.

To avoid cumulation:

- (a) One must know if the drug is eliminated slowly or rapidly.
- (b) Stop the drug administration at the appearance of the first warning symptom.
- (c) Carefully select the form in which the drug is to be administered, and
- (d) Check liver and kidney function before and during drug administration, as even an otherwise non-cumulative drug would produce cumulation in the presence of hepatic and renal damage.

XI. Other drug therapy : Previous or concurrent therapy with certain drugs may result in stimulation or inhibition of the metabolism of other drugs e.g. rifampicin, phenobarbitone, phenytoin and alcohol are potent inducers of hepatic microsomal enzymes and thus, they may increase the dosage requirements of other drugs (See also Chapter 2).

XII. Additive effect : When the total pharmacological action of two or more drugs administered together is equivalent to the summation of their individual pharmacological actions, the phenomenon is termed as an additive effect e.g. combination of ephedrine and aminophylline in the treatment of bronchial asthma.

XIII. Synergism : Facilitation of a pharmacological response by the concomitant use of two or more drugs is called drug synergism. The word synergism is derived from the two Greek words, *ergo* (work) and *syn* (with) and indicates a pharmacologic co-operation. This co-operation usu-

ally results in a total effect greater than the sum of their independent actions e.g. furosemide and intravenous aminophylline; codeine and aspirin; hydrochlorothiazide and reserpine.

If the synergism results in prolongation of action of one of the drugs, it is termed *time synergism*, e.g. procaine and adrenaline combination increases the duration of action of procaine.

The term potentiation is often loosely employed for synergism and should be avoided, as the word 'potentiate' means 'to endow with power', which no drug is really capable of achieving.

XIV. Antagonism : The phenomenon of opposing actions of two drugs on the same physiological system is termed as drug antagonism. Antagonism can be of the following types:

(a) **Chemical antagonism :** In this case the biological activity of a drug can be reduced or abolished by a chemical reaction with another agent e.g. between acids and alkalies; BAL and arsenic.

(b) **Competitive or reversible antagonism :** Here, the agonist and the antagonist compete for the same receptors and the extent to which the antagonist opposes the pharmacological action of the agonist will be decided by the relative numbers of receptors occupied by the two compounds. Competitive type of antagonism can be overcome by increasing the concentration of the agonist at the receptor site, e.g. acetylcholine and atropine antagonism at muscarinic receptors. If the concentration of acetylcholine at the receptor level is increased by the administration of an anticholinesterase, the blockade produced by atropine can be overcome; hence, the antagonism is also termed as reversible antagonism.

A competitive antagonist shifts the dose response curve to the right. The maximal response to agonist is, however, not impaired (Fig. 1.16a).

(c) **Non-competitive antagonism :** In this type of antagonism an antagonist inactivates the receptor (R) so that the effective complex with the agonist cannot be formed, irrespective of the concentration of the agonist. This may happen by

various ways : (a) The antagonist might combine with R at the same site, but the combination is so firm that even higher concentration of the agonist cannot displace it. (b) The antagonist might combine at a different site in such a manner as to prevent the expected characteristic biologic response by the agonist and (c) The antagonist might itself induce a certain change in R so that the reactivity of the site where agonist should interact is abolished. Examples are, acetylcholine and papaverine on smooth muscle; acetylcholine and decamethonium at the neuromuscular junction. In non-competitive antagonism the effect upon receptors may be reversible or irreversible.

Although the agonist curve will shift to the right, the slope will be reduced and the maximum response will diminish. The extent of inhibition produced depends on the characteristics of the antagonist itself and the agonist has no influence upon the degree of antagonism or its reversibility. (Fig. 1.16b).

The term 'physiological antagonism' is sometimes used where a drug when administered reverses the effects of another drug by acting on

different receptors e.g. adrenaline in histamine reaction. Sometimes the term 'functional antagonism' is used to represent the interaction of two agonists that act independently of each other but happen to cause opposite effects, e.g. acetylcholine and adrenaline.

Importance of drug antagonism:

An understanding of drug antagonism is important in

(a) Correcting adverse effects of drug; e.g. ephedrine and phenobarbitone.

(b) Treating drug poisoning; e.g. morphine with naloxone, organophosphorus compounds with atropine.

(c) Predicting drug combinations which would reduce drug efficacy e.g. the penicillin and tetracycline combination is inferior to penicillin alone in pneumococcal meningitis.

XV. Drug tolerance : When an unusually large dose of a drug is required to elicit an effect ordinarily produced by the normal therapeutic dose of the drug, the phenomenon is termed as drug tolerance. Drug tolerance is of two types.

(1) True tolerance: seen on both oral and

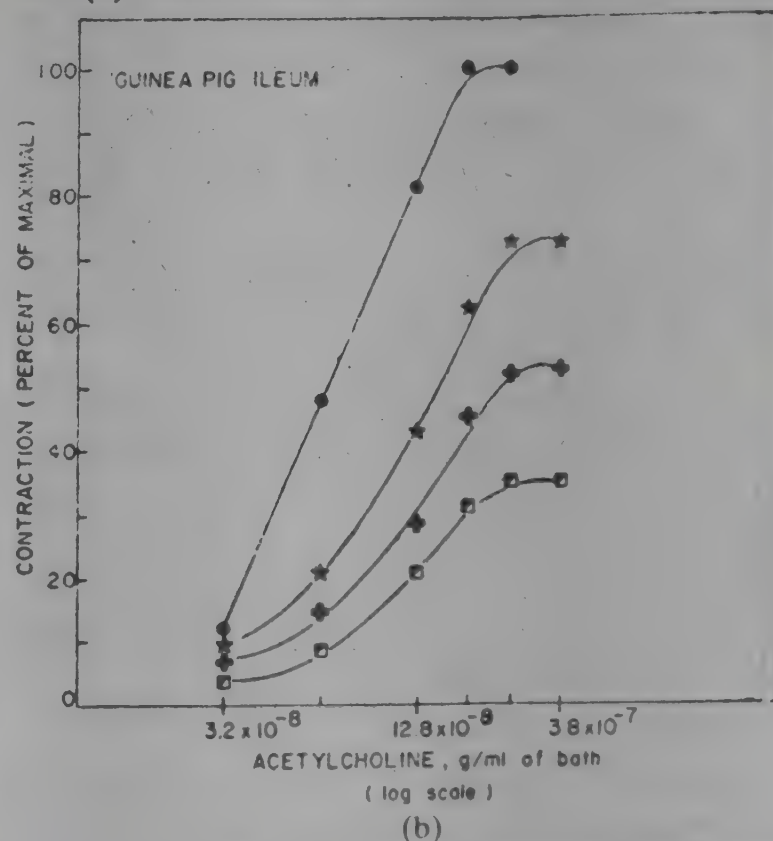
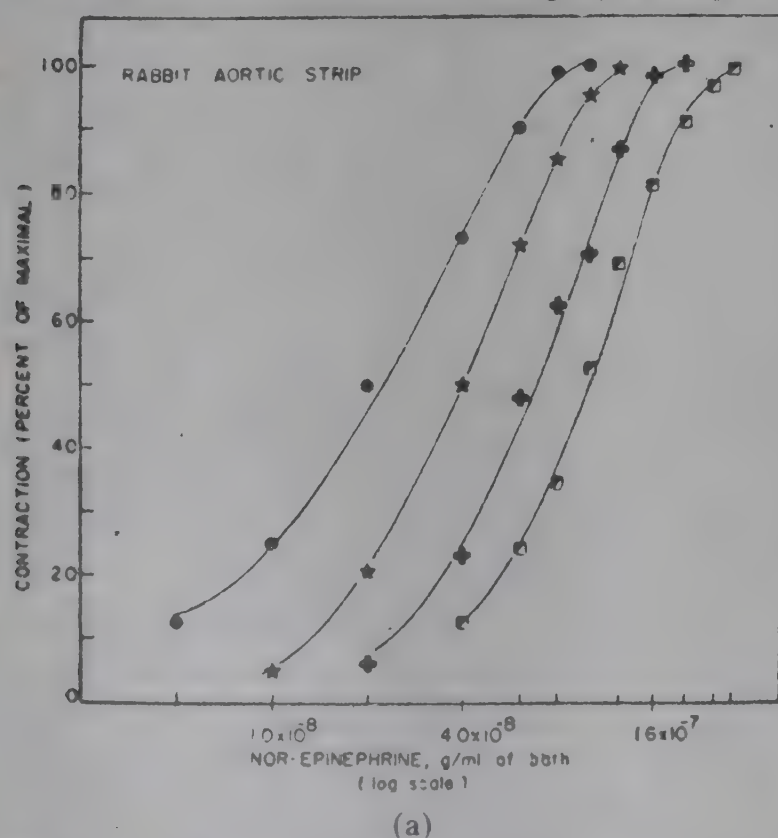


Fig. 1.16 : (a) Characteristic of competitive antagonism between noradrenaline and an antagonist. Black dots denote the control curve. Subsequent curves are drawn with increasing concentrations of the antagonist. Note that the curves are almost parallel and maximum response could be obtained with noradrenaline on each occasion.

(b) Characteristic of non-competitive antagonism. Note the decrease in response to acetylcholine following the increase in antagonist concentration.

parenteral administration of the drug.

(2) **Apparent or pseudotolerance:** confined only to the oral route of administration of the drug.

(1) **True tolerance:** This can be subdivided into : (a) Natural and (b) Acquired.

(a) **Natural:** This is seen in various animal species and also among the various human races. It includes:

(i) **Species tolerance:** Certain animal species can tolerate certain drugs in quantities lethal to man e.g. some rabbits can tolerate large quantities of belladonna. This is attributed to the enzyme atropine esterase in the rabbit liver and plasma, which rapidly detoxifies belladonna. Invertebrates can tolerate large quantities of strychnine; and, rodents can withstand large amounts of histamine.

(ii) **Racial tolerance:** A solution of ephedrine instilled into the conjunctival sac of the Caucasians produces prompt dilatation of the pupil but in Negroes it may not produce any dilatation at all.

(b) **Acquired tolerance:** This tolerance, unlike the racial or species tolerance develops only on repeated administration of a drug. Many drugs, including opiates, barbiturates, nitrites and xanthines produce tolerance. Tolerance is sometimes desirable e.g. barbiturates, when used in the treatment of epilepsy, produce tolerance for their soporific but not for their antiepileptic effect. Generally however, tolerance is undesirable.

Tissue tolerance: In this type, the development of tolerance is confined to certain effects or to certain systems e.g. morphine produces tolerance for its euphoriant effect but the pupils and the gastrointestinal tract never become tolerant. Thus, the same dose of morphine invariably produces pin-point pupils and constipation but may fail to produce euphoria.

Cross tolerance: If an individual initially develops tolerance to a drug belonging to a particular group, he also shows tolerance to other drugs belonging to the same group. This phenomenon is known as cross tolerance. Thus, an individual tolerant to the vasodilator effect of glyceryl trinitrate is also tolerant to pentaerythri-

tol tetranitrate, belonging to same group. Another well known example of cross tolerance is that between alcohol and the general anaesthetics like ether.

(2) **Apparent or pseudotolerance:** The feudal kings, much worried about poisons, were often in the habit of taking small doses of poisons by mouth. This apparently rendered them immune to oral poisons but poisoning could occur if any other route were chosen. This tolerance to the oral administration of the poison is probably due to the local changes developed by the gastrointestinal tract which prevents the poison from getting absorbed into the systemic circulation.

Mechanism of development of true tolerance: The phenomenon of tolerance can be divided into two classes. The first called as '*dispositional tolerance*' is due to changes in drug absorption, distribution, excretion and metabolism leading to decreased intensity and duration of contact between a given drug and the target tissue. Thus, the barbiturates after repeated administration enhance their own detoxification by stimulating the microsomal enzyme systems in the liver. Certain rabbits show tolerance to belladonna due to its rapid metabolism. Phenylbutazone is excreted much more rapidly in the rodents, dogs and cats than in human beings and these animals are relatively tolerant to phenylbutazone.

The second type referred as '*functional tolerance*' or pharmacodynamic tolerance is probably due to changes in the properties and functions of the target tissue, that make them less sensitive to a given drug concentration. Thus, it is associated with some cellular changes. With some drugs this may be related to a decrease in drug responsive receptors. By means of careful experiments with compounds like morphine and the barbiturates, it has been demonstrated that the cells of the central nervous system, which usually develop tolerance to these drugs, become capable of normal physiological functions in the presence of high concentrations of these drugs. For mechanism of tolerance to nitrates, see Chapter 27.

The adaptive mechanisms which enable the tolerant cells to withstand toxic drug concentra-

tions are not clearly understood.

Tachyphylaxis : Tolerance to drugs as described above usually takes quite some time to develop. However, with certain drugs like ephedrine, tyramine, amphetamine and 5-hydroxytryptamine, tolerance may appear rapidly in isolated preparations as well as in the intact animals. Thus, if any of these drugs is administered repeatedly, at very short intervals, the pharmacological response elicited decreases progressively. This phenomenon is known as *tachyphylaxis* or *acute tolerance*. For example, if tyramine is given repeatedly to an animal at intervals of about 10-15 minutes the pressor effect becomes progressively less (Fig 1.17). Similarly, repeated doses of ephedrine at short intervals, in the treatment of bronchial asthma may produce diminishing response.

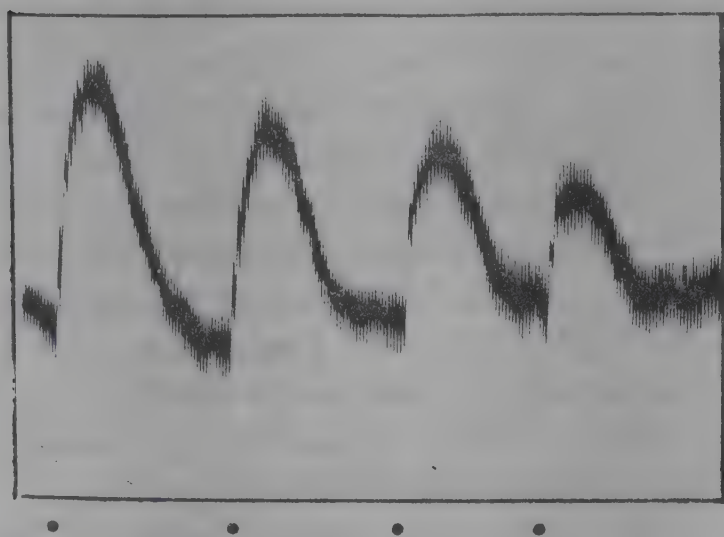


Fig. 1.17 : Effect of repeated doses of tyramine on B.P. in anaesthetized dog. Black dots denote administration of the same dose.

Various mechanisms are responsible for the appearance of tachyphylaxis. In case of tyramine, it is due to depletion of the noradrenaline stores from the sympathetic nerves. However, with sympathomimetics like ephedrine and amphetamine, tachyphylaxis can occur without appreciable depletion of the noradrenaline stores. Tachyphylaxis probably can occur if the drug dissociates only slowly from its combination with the receptor, thus continuing receptor blockade while losing its intrinsic activity and hence its pharmacological effect. It has been observed that

tachyphylaxis or refractoriness with isoprenaline is accompanied by a decline in beta receptor number while receptor affinity for the agonist remains unaltered. Such refractoriness may have relevance to human disease or treatment states. With many drugs, however, tachyphylaxis is probably due to some unidentified 'adaptive response' of the tissue concerned.

XVI. Drug dependence : Repeated administration of certain drugs may cause a habit and dependence. If the habit forming agent is not made available to the habitue, he develops withdrawal symptoms characterized by psychic disturbances like headache, restlessness and emotional upset and/or convulsions and vasomotor collapse. W.H.O. has defined drug dependence as "A state, psychic and sometimes also physical, resulting from the interaction between a living organism and a drug, characterized by behavioural and other responses that always include a compulsion to take the drug on a continuous or periodic basis in order to experience its psychic effects and sometimes to avoid the discomfort of its absence. Tolerance may or may not be present. A person may be dependent on more than one drug". A condition in which a drug produces "a feeling of satisfaction and a psychic drive that require periodic or continuous administration of the drug to produce pleasure or to avoid discomfort" is called *Psychic dependence*. In case of *Physical dependence*, the body "achieves" an adaptive state that manifests itself by intense physical disturbances when the drug is withdrawn. The term 'addiction' was formerly used to denote the phenomenon involving both psychic and physical dependence on drugs. Its characteristics include an overpowering desire (compulsion) to continue taking the drug, a tendency to increase the dose and a high tendency to withdrawal symptoms. Compulsive drug use is commonly but not necessarily associated with the development of tolerance and physical dependence. There are many drugs where tolerance and physical dependence develop after chronic use; but they are not self administered and used compulsively by man.

Man has long sought ways of enhancing his pleasure and of easing his discomforts. Various agents are consumed to achieve this goal. Commonly used beverages like tea and coffee stimulate the central nervous system and are capable of producing drug dependence but this is not necessarily harmful in itself. Tobacco on the other hand is a dependence-producing agent capable of causing physical harm to the user although it produces relatively little stimulation of the CNS. Most of the drugs used by the addicts have predominantly central nervous system effects. Such drugs like opiates, barbiturates, alcohol and cannabis all produce a feeling of well-being in the individual. This peculiar sense of well-being is termed euphoria and contributes considerably to the development of dependence. However, when exposed to these drugs under similar environmental influences, all the recipients do not develop dependence. It is not clear why some individuals stop after initial experimentation. Others continue drug use but do not become dependent and still others become compulsive drug users or drug addicts. But majority of those who develop dependence have some psychological problems; only 5.5 per cent are probably normal. Besides the user's personality, availability of the drug plays an important part in the development of drug dependence. Thus, for the development of severe dependence, both the 'seed' and the 'soil' are required.

A potential addict may start and continue taking a dependence forming drug : (1) following its medicinal use; (2) to satisfy curiosity about drug effects; (3) to achieve a sense of belonging, to be 'accepted' by others in the group; (4) to express hostility or independence; (5) to have pleasurable (euphoric), new, thrilling or even dangerous experiences; (6) to gain an improved understanding or creativity; (7) to escape from reality, to have a dreamy state; and (8) to achieve a sense of relaxation from stresses and tension of life. The experience achieved by the individual under the influence of the drug is so impressive that he develops a craving for it and finds it difficult to

give it up. These drugs themselves are powerful reinforcers. Hence, these drugs are also called 'Masterful drugs'. Among the more important factors that appear to facilitate the initiation of drug use are : (a) ready availability of drugs as in case of doctors and medical students; (b) general public acceptance of the use of mood modifiers such as alcohol; (c) increasing mobility particularly of youth; (d) peer group pressure; (e) an abundance of information about drug effects and sources; (f) lack of adequate publicity given to harmful effects of these agents; and (g) unstable or broken homes, sociocultural pressures and social ills.

The exact mechanism of drug dependence is not known. Alteration of the cellular metabolism of the CNS is a prime factor in the development of drug dependence. Other systems may become tolerant to the drug but only the central nervous system is capable of developing physical dependence. Withdrawal of the drug under these circumstances produces distorted homeostasis and this results in the development of a *withdrawal syndrome* or an *abstinence syndrome*. The withdrawal syndrome may vary from a mild to a severe one sometimes resulting in fatality. All the drugs that cause physical dependence are depressants of the central nervous system. The symptoms of withdrawal syndrome are usually characterized by rebound effects in those same physiological systems that were initially modified by the drugs. Thus, general CNS depressants on withdrawal cause hyper-excitation while withdrawal of central stimulant amphetamine produces weakness, lack of energy, hyperphagia and depression. Withdrawal symptoms due to drugs with long half-lives e.g. phenobarbitone are usually less severe but more protracted.

It is highly desirable that drugs which are likely to be administered over a prolonged period should be screened for their dependence liability in animals.

Drug dependence once developed, is difficult to treat. To achieve any success, complete co-operation of the individual is vital. The principles

of treatment are :

- (a) Gradual or sudden withdrawal of the drug.
- (b) Substitution therapy.
- (c) Psychotherapy and occupational therapy.
- (d) Specific drug therapy e.g. antabuse in alcohol addiction.
- (e) Correction of nutritional deficiencies.
- (f) Community treatment and rehabilitation.

The treatment should preferably be carried out in a specialized institution under expert guidance.

Table 1.4: Important drugs known to cause dependence.

- I Drugs that cause severe psychic as well as physical dependence :**
 - a: Opiate or morphine type :**
Morphine and its congeners like codeine, dihydromorphinone (Dilaudid) and heroin. Synthetic morphine substitutes such as meperidine (pethidine) and its congeners, methadone and its congeners, morphinan compounds, phenazocine and diphenoxylate (Lomotil)
 - b: Alcohol-barbiturate type :**
Ethyl alcohol, barbiturates, paraldehyde, chloral hydrate, meprobamate, glutethemide, methylprylon, ethinamate, ethchlorvynol, benzodiazepines and methaqualone.
- II Drugs that cause definite psychic but mild or questionable physical dependence :**
 - a: Opiate antagonist type :**
Morphine antagonists like nalorphine; morphinan antagonists like levallorphan; and benzazocine antagonists like cyclazocine.
 - b: Amphetamine type :**
Amphetamine, methamphetamine and phenmetrazine. Piperidines like methylphenidate and pipradol.
- III Drugs that cause only psychic dependence ;**
Cocaine, LSD, psilocybin, mescaline, cannabis (marijuana, hashish), nicotine (tobacco), caffeine (coffee, tea).

ASSAY

Assay is the estimation of potency of an active principle in a unit quantity of the preparation. It can be :

(I) Chemical, (II) Biological and (III) Immunological assay.

I. Chemical assay: Here, the concentration of

the active principle is estimated by means of a chemical method, e.g. the salicylates, sulfonamides, and many others. It is the most commonly used procedure. The useful techniques are spectrophotometry, fluorometry, gas chromatography, mass spectrometry and high pressure liquid chromatography.

II. Bioassay: Bioassay is the determination or estimation of the amount of biological activity in a unit quantity of the preparation.

Indications for bioassay:

- (a) When the chemical composition is not known but the substance has a specific action e.g. long acting thyroid stimulator (LATS).
- (b) When there is no simple chemical means of ensuring a product of constant composition.
- (c) When the chemical assay method is too complex or insensitive e.g. adrenaline and histamine can be bioassayed in microgram quantities.
- (d) When drugs which differ in composition but have the same pharmacological action e.g. the digitalis glycosides obtained from various sources.
- (e) When the active principle is unknown, cannot be isolated easily or may undergo decomposition during isolation procedures e.g. peptide hormones.

International Unit (I.U.): Internationally agreed upon standards are necessary to compare the *potency* of the various biologically assayed compounds.

It is unsatisfactory to designate a unit of a particular drug as that amount which causes a particular effect i.e. to express the potency of drugs in terms of cat, mouse or rat units. The reason is that the biological effects of drugs vary from animal to animal, from time to time, and from laboratory to laboratory.

If it is not possible to purify chemically the substance to be bioassayed, a stable standard solution has to be employed for comparison. Standards for sera are held at the State Serum Institute, Copenhagen, the National Institute for Medical Research at Mill Hill, U.K. and by the W.H.O. An International Unit is defined as a

particular quantity of the standard preparation (one International Unit of tetanus antitoxin is 0.1547 mg. of a preparation held in Copenhagen).

Principles of bioassay

(a) The specific effect produced by the active principle to be bioassayed must be the same in all animal species. An exception is the liver preparations used formerly in the treatment of pernicious anemia. These preparations cannot be bioassayed in experimental animals as pernicious anemia occurs only in human beings.

(b) A certain quantity of a drug produces the same degree of pharmacological response in the same animal or animals of the same species, provided the other conditions remain constant e.g. adrenaline will always elicit the same degree of rise in blood pressure when given in the same dose, in the same animal and under identical conditions.

(c) The reference standard must owe its activity to the principle for which the sample is being bioassayed.

(d) The activity assayed should be the activity used therapeutically.

(e) Problems of individual variation must be minimized.

(f) It must be remembered that the bioassay may measure a different aspect of the same substance as compared to the chemical assay as in the case of testosterone and its metabolites.

Methods of bioassay: Bioassay is a measure of the concentration of the specific active ingredient of a crude drug and is performed by determining the amount of the active ingredient required to produce a definite effect on a suitable test animal or organ under standard conditions. Thus bioassays can be performed on whole animals either singly or in groups or on isolated tissues. The important methods are:

(1) **Direct comparison on same tissues:** Here, the concentration of the unknown is determined by:

(a) *Interpolation:* Wherein a log dose response curve is plotted initially by using at least 4 submaximal concentrations of the standard. The concentration of the unknown is then read from

the graph. See Fig 1.12 (b).

(b) *Matching:* A constant dose of the sample is bracketted by a varying dose of the standard, till an exact matching between the sample dose and a particular dose of the standard is achieved. This method, however, is rather inaccurate and it is difficult to estimate the margin of error e.g. histamine bioassay on the guinea pig ileum, posterior pituitary assay on the rat uterus.

(c) *The four point assay :* Which incorporates the principles of interpolation and matching and hence, is the most accurate of the three methods.

(2) **Direct assay on several animals:** In this method, the dose of the sample required to elicit a particular pharmacological effect (ED_{50} or LD_{50}) is measured e.g. death in guinea pigs. This dose is known as the 'tolerance' or 'threshold dose'. Ratio of the threshold dose of the sample and the threshold dose of the standard gives the relative potency of the sample in terms of the standard. To employ this method, the drug must produce clear-cut pharmacological effects, e.g. digitalis bioassay in guinea pigs.

(3) **Indirect assays :** If the potency of the sample is estimated by comparing the dose response curve (more often the log dose response curve) of the sample with a similar curve of the standard, the method is referred to as an indirect assay.

Ergot preparations, when injected in the white leghorn cock, produce vasoconstriction and this results in a bluish discoloration of the comb. The colour intensity varies with the dose and this effect may be employed for bioassay of crude ergot preparations by the indirect method.

To avoid the influence of extraneous factors such as bias, inherent activity of the animal etc., on the bioassay, various randomization techniques like cross-over designs (subjecting the 'standard' and the 'sample' animal groups to the sample drug and the standard drug respectively) are employed. The results obtained are subjected to statistical analysis and the margin of error is calculated. Allowance must be made for this error when expressing the potency of the sample.

The bioassay procedures must satisfy the fol-

lowing requirements:

- (a) High *sensitivity* and *accuracy*.
- (b) High *specificity*, e.g. the ileum of the guinea pig contracts with both acetylcholine and histamine. The tissue, therefore, has to be atropinised for the bioassay of histamine.
- (c) *Reproducibility* : The pharmacological response with the same dose should remain the same under identical conditions.
- (d) *Stability*: The animal or the tissue should remain 'bioassay fit' for a sufficiently long time.
- (e) *Easy availability* of the animals.

Certain important bioassays:

- (i) **Whole animal:**
 - (a) Noradrenaline: Spinal cat, rise in blood pressure.
 - (b) Digitalis: Guinea pig, death due to cardiac arrest.
 - (c) Vasopressin: (i) Anaesthetized rat, rise in B.P. and (ii) Hydrated rat, reduction in the urine output.
 - (d) Estrogens: Ovariectomised female rat, vaginal cornification.
 - (e) Vitamin D: Rat, alleviation of the rachitic state.
 - (f) Insulin: Mice, hypoglycemic convulsions or death.
 - (g) d-tubocurarine: Rabbit, head drop due to paralytic relaxation of the skeletal muscles of the neck.

(ii) **Isolated tissue:**

- (a) Acetylcholine: (i) Frog, rectus muscle, contraction, and (ii) Leach dorsal muscle, contraction.
- (b) Histamine: Guinea pig ileum, contraction.
- (c) Adrenaline: Rat uterus in diestrus, relaxation.
- (d) Oxytocin: Rat uterus estrogen primed, contraction.

(e) Leutinizing hormone (L.H.) : Ability to stimulate testosterone synthesis *in vitro* by isolated Leydig cells of testis.

(iii) **Micro-organisms:**

Tetracycline: Inhibition of the growth of *Bacillus pumilus*; Vitamin B₁₂ growth of *Euglena gracilis*.

Biostandardization: Comparison and adjustment of the strength of the sample with that of the standard under rigidly controlled conditions is termed as biostandardization.

This is necessary to regulate the doses of crude drugs such as tincture digitalis which contain variable quantities of the active principle.

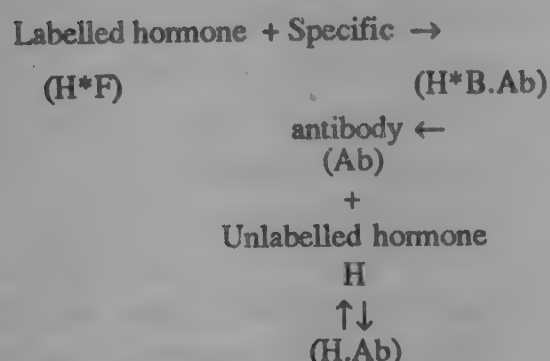
It must be emphasized that sensitivity and specificity make the bioassay a very important tool in pharmacology. In fact, it has proved an economic and convincing way of examining the presence of a number of endogenous compounds of pharmacological and pathological importance such as hypothalamic factors, prostaglandins, encephalins and vitamin B₁₂.

III. Immunoassay : Many immunological methods have been developed to estimate hormones. One of the widely used method is radioimmunoassay. It started with the observation that intravenously injected radioiodine-labelled insulin (¹³¹I-Insulin) persists for a longer time in the circulation in patients who have previously received insulin therapy, as compared to normal subjects. This is because the labelled insulin gets bound to a circulating antibody, formed as a result of previous insulin therapy.

Unlike the bioassay *in vivo* or *in vitro*, the radioimmunoassay is physico-chemical assay and depends upon the reaction between a hormonal antigen and its specific antibody in the test tube. The antibodies used are generally obtained from the sera of animals, such as rabbits, which have been previously immunized by repeated injections of the pure hormone (antigen). The principle of the radioimmunoassay can be summarized by a set of competing reactions in a mixture containing radiolabelled hormone, antibody and unlabelled hormone (either standard or unknown).

Radioiodine-labelled hormone H* is designated as 'unbound' or free (F) or 'bound' (B). Binding of the labelled hormone to the antibody is competitively inhibited by the unlabelled hormone. Hence, the per cent binding of labelled hormone or alternatively B/F ratio progressively

diminishes as the concentration of the unlabelled hormone increases.



A standard curve is obtained by plotting B/F ratios against known concentrations of unlabelled hormone in a set of standards prepared for the assay. The biological material (plasma) containing an unknown quantity of the unlabelled hormone is allowed to react with the mixture of labelled hormone and the antibody under the same set of conditions as the standards. The B/F ratio is obtained and the concentration of the unlabelled hormone in the plasma is read off the standard curve (Fig. 1.18).

Using this principle, plasma concentration of various hormones, other biological substances and drugs can now be measured easily and accurately.

It is now possible to measure minute quantities of circulating hormones and other biologically active substances by the radio-immunoassay and certain symbols are now commonly used to express the small quantities such as :

Fraction of g.	Prefex	Symbol
10^{-3}	milli	mg
10^{-6}	micro	μg
10^{-9}	nano	ng
10^{-12}	pico	pg
10^{-15}	femto	fg
10^{-18}	atto	ag

It must be emphasized, however, that

immunoassay methods measure all the immunologically active components which may not necessarily be active biologically. Further, the reliability of the results depends largely on the specificity of the antiserum (antibody) which in turn depends upon the purity of the hormone (antigen) used for immunizing the animals. When

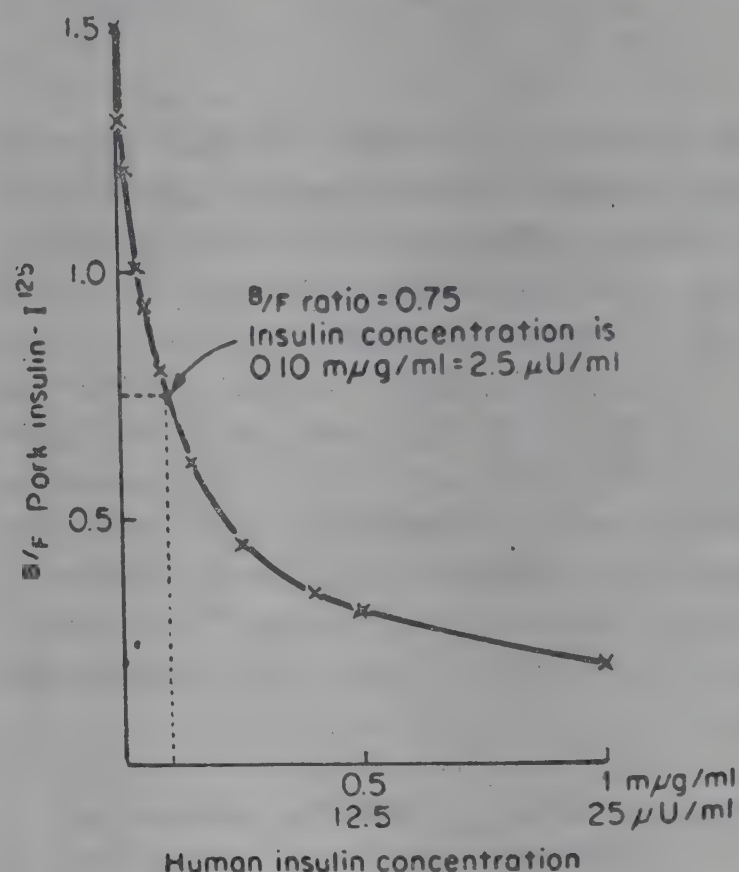


Fig 1.18 : A standard curve for radioimmunoassay of insulin (Reproduced, with permission, from *Diabetes Mellitus : Theory and Practice*, by M. Ellenberg & H. Rifkin, 1970, McGraw-Hill Book Co., N.Y.)

the results of such an assay differ from those obtained by the biological assay, the latter should not be ignored.

Radio-receptor assays have been developed embodying the principles of both bioassay and radioimmunoassay; they are more sensitive and more specific than the radioimmunoassays.

Certain enzymes such as alkaline phosphatase and penicillinase are now used in place of radioactive iodine to label hormones; such assays are called Enzyme Linked Immunosorbent Assays (ELISA).

2 Evaluation of Drugs in Man, Drug Prescribing and Drug Interactions in Man

The ultimate aim of pharmacological studies in animals is to find out a therapeutic agent suitable for clinical evaluation in man. No doubt, animal studies provide analogies and serve as useful models. But certainly a cat or a rat cannot act as an ideal model for man. The administration of a biologically active agent to human beings is associated with an element of risk which cannot be predicted by even the most careful and exhaustive animal experiments. Hence, the drug has to be carefully evaluated in man himself for its safety and efficacy before it is accepted for therapeutic use.

Who should carry out the evaluation?

The first evaluation of a new drug in humans should be carried out by a clinical investigator who has the requisite 'know how', necessary facilities and time to undertake such work. Such a clinical investigator with an adequate background in interpreting animal studies and who uses drugs cautiously and critically in humans, with continuing analysis of the result achieved is called a Clinical Pharmacologist. Unimaginative screening of drugs in man is not clinical pharmacology. While evaluating, one should also study critically the effects of the new drug on various body systems. *Clinical pharmacology*, therefore, involves the study of various aspects of drug action and metabolism in humans, both in health and in disease and, therefore, is a discipline which is a part of medicine as a whole. Ideally, therefore, the Clinical Pharmacologist should be a combination of a pharmacologist and a clinician. However, Clinical Pharmacologists can be clinicians working in the disciplines of medicine, therapeutics,

cardiology, anaesthesiology and even surgery. Obviously, one should restrict such work to the field of one's specialization where one has the requisite experience and full knowledge of the ever increasing advances in the subject. This is essential because the safety and effectiveness of new drugs solely depend on his strict, unbiased and uncompromising adherence to the highest scientific standards. More than the equipment and finances it is the honesty and calibre of the investigator involved that matters most.

Justification for the Clinical Evaluation:

Prior to any clinical evaluation the investigator should obtain reasonably clear answers to three important queries :

- (1) Is the data from animal studies adequate?
- (2) What is the probable risk involved in giving the drug to humans? Is it worth the risk?
- (3) Is there any need for a new drug in the disease under consideration and if so is the new remedy promising, as seen from animal studies?

A new drug with a completely novel structure with novel pharmacological action is very rarely born. Many times it is discovered by chance observation as in the case of penicillin, antidiabetic sulfonylurea derivatives and oral diuretics. Most of the new drugs prepared are related to, or are very similar to, known drugs. Obviously, the benefit offered by such imitative agents to the patient is generally small and sometimes the new drug may even be worse than the well tried parent compound. The clinical studies with such imitative ('me-too') drugs are justifiable only if the other established drugs are far from ideal and

if animal studies indicate distinct biological advantages over the parent compound in clearly defined terms. Effectiveness of the drug in very small doses, in itself, is not a justification for human studies, when the toxic effects are known to run parallel with 'higher potency'. Such a preparation would be difficult to dispense for human consumption and difficulties in regulating its dosage would be enormous. A clinical trial is justified if the new drug is shown to be potentially less toxic without significant reduction in its therapeutic efficacy.

A drug with a completely new structure and/or a new mode of action, if found reasonably safe in animal studies, certainly deserves to be studied clinically. Human pharmacological studies with such a compound with particular reference to its mode of action, biochemical changes produced and its actions on various systems of the body may eventually lead to formulation of a new potentially useful structure. A new compound with a related but widely different chemical structure is likely to produce more novel actions than a closely related imitative compound and hence, deserves clinical studies. In all these cases the animal experiments should demonstrate the probable safety and the potential biological advantage of the compound.

Interpretation of animal data :

No tests on animals, however meticulous and prolonged, can ever prove with absolute certainty the efficacy or safety of a new drug in man. Animal pharmacological studies would only indicate the probable beneficial and toxic effects that may be expected during human experiments; one must balance the probable benefits against possible harm that could occur. Almost every drug with biological activity will produce some adverse effects. Drugs that are claimed to be absolutely harmless are also likely to be therapeutically useless.

Toxic actions disclosed in the animal studies should always be looked for during drug trial in man. However, although such studies can eliminate obvious toxicity, certain serious adverse

reactions such as allergy, neurological toxicity and blood dyscrasias are difficult to detect in animals. It is known that pharmacokinetics of a drug differs both qualitatively and quantitatively in different species. Thus, penicillin, a potent and reasonably safe antibiotic used in humans, can produce fatal toxicity in guinea pigs even in small doses. Further, the animals used in toxicity studies are not necessarily suffering from the disease for which the drug would be used in humans. Hence, such studies should be carried out in many species and, if possible, in both healthy and diseased animals. In toxicological experiments high doses of the drug should be used to bring out the possible toxic effects and subacute and chronic toxicity studies in animals must always precede the chronic administration of the drug in man. Such pharmacodynamic and pharmacokinetic studies in animals help the physician to understand and treat the effects of over-dosage of drugs in man.

Subjective responses like nausea, headache, tinnitus, weakness and loss of libido due to a new drug are difficult to discover by animal studies. Some of these effects, if severe, could considerably reduce the therapeutic utility of the drug in routine practice.

The relative usefulness of animal studies would be decided by the relevance of animal tests to the human condition, where drug would be used. Thus, the animal studies regarding a potential diuretic or hypotensive or an antibacterial drug will provide more useful information than those regarding drugs supposed to be effective in mental diseases in humans, since similar conditions cannot be experimentally produced in animals.

It is necessary that all the animal data be evaluated jointly by the pharmacologist, the biochemist and the toxicologist to determine the suitability of the drug for initial studies in man.

While deciding the dose to be administered for the first time in humans, it should be remembered that dose in smaller animals tends to be larger than that in larger animals and dosage schedule based on animal body weight basis should never be

applied to human studies. If possible, the pharmacological actions of a new drug in humans should be controlled by measuring blood levels guided by similar estimations done in different species of animals. The clinical investigator should discuss with the pharmacologist the toxicity observed in various animal species and decide the probably effective and reasonably safe dose for human administration. It has been suggested that during the first cautious trial in humans, about 1/6th to 1/8th of the predicted effective dose should be administered and then increased gradually.

Clinical Evaluation :

It is essential to have information about the chemical and pharmaceutical properties (such as solubility and stability) of a new product before it is biologically tested.

(A) The first clinical evaluation (Phase I testing) in humans is undertaken to find out :

- (1) The safety and toxicity of such preparation.
- (2) Biologic activity and tolerability of the drug and the dosage range.
- (3) Other pharmacodynamic effects that it may produce, unrelated to its therapeutic action.
- (4) Pharmacokinetic information.

Such studies are carried out at limited centres by competent investigators. The aim is to obtain precise information from the smallest number of volunteers/patients in the minimum possible time. Both subjective and objective evaluation are done along with relevant laboratory studies to detect unexpected but not uncommon biochemical changes associated with toxicity. Usually these studies are initially carried out in healthy volunteers. Once the safety is proved in volunteer studies, further studies may be carried out in pathological states which the new drug is expected to modify. The prime requisites for such an evaluation are :

- (1) precise diagnosis,
- (2) uniformity of patients with respect to age, sex and severity of the disease, and

(3) a clear index of accomplishment relevant to the therapeutic objective.

The clinical investigator must decide how far it is ethical to withhold a known treatment for the sake of trial with a new drug and whether any additional ancillary therapy is needed. If other known drugs are also to be administered simultaneously for some reasons it is necessary to watch for abnormal reactions, if any, due to drug interactions. The first trial carried out with the above mentioned objectives need not be 'a controlled trial' in the usual sense of the term.

An initial drug trial is usually carried out in healthy volunteers or patient volunteers and rarely in non-volunteer patients as in the case of mental diseases. The problem of consent in clinical trials is complex; but in case of healthy volunteers and in patients where the subjects are not likely to be benefited by the drug, prior consent should always be obtained. Children and women of the child-bearing age should not be included in the earliest studies with new drugs. Further, the study should be approved by the ethics committee.

In certain fields like endocrinology, or infectious diseases where the aetiopathology is precisely known, the clinicopharmacological studies with new compound could be precise, quantitative and predictable e.g. value of penicillin in pneumonia and thyroxine in hypothyroidism. But often such knowledge about the disease is not available and the natural history of the disease is such that the correct assessment of a new drug becomes difficult as in atherosclerosis, psychiatric disorders and peptic ulcer. Clinical assessment is also difficult in case of drugs expected to produce subjective relief of symptoms such as pain, nausea, anorexia and sleeplessness. In such circumstances controlled clinical trials are absolutely necessary to prove or disprove the therapeutic usefulness of the drug as well as for comparing a new drug with the previously established drug.

(B) After the satisfactory initial trial, further evaluation is carried out in larger number of

patients to get more data on metabolic activity and toxicity, and to determine final dosage form of the drug (Phase 2). This is followed by Phase 3 studies which include controlled clinical trials. A *controlled clinical trial* may be defined as one where a new drug therapy is compared with the previously established therapy or placebo therapy, under standardised conditions. It is designed to ensure that the comparisons made are as precise, as informative and as convincing as possible. Such studies are mainly conducted in two ways :

(1) Where drug is given to one group and results are compared with those from the other group (the control group).

(2) Where the drug therapy is alternated with control therapy, either with an inert substitute or with the previously established drug, in the same patient.

In the first method which is most widely employed, patients are allocated to various groups. This allocation procedure is very important. In order to balance the groups and to avoid any bias, allocation should be carried out by randomization by a person who is completely unaware of the therapy allotted to an individual group. One of the groups gets the new treatment while the other receives control therapy, with either

(a) a previously established drug or

(b) an inert agent administered in a similar form and in similar way as the drug under consideration.

When both the evaluating clinician and the subject are unaware of the nature of the drug being administered, the procedure is called a *double blind controlled trial*. It effectively reduces the influence of extratherapeutic factors. In case any laboratory investigations are involved, the specimens should be submitted to the laboratory under a code number. The treatment is decoded only after the trial is over.

In the second method the patient acts as his own control. This reduces the chances of erroneous results obtained due to individual variation amongst the patients. Allocation of the patient to new therapy first or to control treatment first is

decided by *randomization* and the evaluating clinician may not know the sequence of drug administration before completion of the trial. As in the first method such a study can be made a double blind controlled trial.

(C) Finally, the results of such controlled trials at a few centres are confirmed by broad multicentric clinical trials at many centres before the drug is recommended for general use.

Even after such precautions, the real clinical status and the nature and frequency of adverse reactions often becomes apparent only after the drug is released for general use. Therefore, careful monitoring must continue even after the drug is marketed. It is during this phase, that astute observation by practising doctors leads not only to early detection of adverse reactions but also to recognition of unanticipated additional benefits which result in additional, secondary uses for drugs e.g. intraocular beta blockers for glaucoma and minoxidil for baldness.

Role of Placebo:

In both Phase 2 and 3 studies many times a pharmacologically inert substance is used as a placebo to eliminate the possible benefit of the drug solely due to chance. Placebo is a Latin term which means "I may please you". The placebo effect is an effect attributable to a medicament as a procedure and is not due to any specific pharmacodynamic property of the substance, for the condition being treated. Placebo effect may be defined as "how the patient's perception of treatment influences his/her response".

A placebo preparation is usually a pharmacologically inactive substance like starch or lactose. However, occasionally it may be a drug that is pharmacologically active but in a different situation. In fact, even when an active drug is used for cure, its placebo effect often satisfies the patient long before the drug causes a cure. It is well known that the patient as well as his relatives get some immediate relief as soon as the doctor's medicine is administered, irrespective of its drug content. This is because of their faith in the doctor

that things will go well in his hands.

Placebos are used in clinical trials to eliminate the effect of bias of the physician and the patient, particularly in evaluating a new drug claimed to be effective in conditions like bronchial asthma, hypertension, angina pectoris, pain and psychiatric disorders. In such cases the placebo should be indistinguishable from the active medicament in physical properties like colour, smell, taste and form.

Placebos can often produce relief of subjective symptoms associated with psychological disturbances. These include relief from anxiety, headache, pain, insomnia and breathlessness. Hence, placebos are often employed in the treatment of certain diseases where the psychic element is suspected to be responsible for subjective symptoms. Objective responses such as increase or decrease in neutrophils and eosinophils are rarely seen with placebos.

When administered for its therapeutic effects, the placebo preparation must appear relevant to the illness, be harmless and should preferably conform to the patient's expectations. To be very effective, the 'potency' of the preparation must be shown by some signs such as strong taste, a colourful capsule or a tablet of odd shape and sometimes even by obvious but harmless side effect like coloured urine.

Placebo effect may be modified by :

(a) *Personality of the physician* : Reassurance and optimistic outlook often achieve a better effect. "The doctor himself must inspire confidence. It is difficult to define this quality. It does not lie so much in what is said as in the doctor's shape and bearing, and in those instinctive signs whereby one animal unknowingly conveys its mood to another. Some have it and some do not. In this respect, the hospital specialist is in an easier position than the G.P. because he is backed by a temple of healing, which is clearly nearer the seat of power than a wayside shrine. Since few doctors are good enough actors to stimulate the confidence they do not have, it often happens that one who is kind and credulous is a

better healer than another who is informed and critical. Placebo reactions go faster when both parties have faith and in this respect knowledge is an inhibitor. It follows that anyone who wants to know whether a cure was due to a drug, and therefore, reproducible, would have to observe the ceremony conducted by sceptics". (Prescribers J., 8, 84, 1968). Further, "People need a doctor. Not merely to tell them that symptoms presage nothing serious, that nothing is the matter; but, whether or not anything is the matter, to tell them that they should do certain things under medical instruction - cut out coffee, avoid pepper, take off the back brace and then put it back again. reassurance is not always enough what is needed is constant, patient instruction, the innumerable placebos hailed as possible sovereign remedies. But at all times prescribed with compassion. For the doctor..... is an essential substitute in an irreligious age, for that Someone who is supposed to watch over us" (Alistair Cooke in "The Patient Has the Floor").

(b) *Personality of the patient* : Some individuals are amenable to suggestions. They take their medicines regularly and like to try every new compound available in the market. Such people are termed *placebo reactors* and since a placebo acts by suggestion, derive benefit from the use of placebos. Neurotics are great placebo reactors while depressed or psychotic subjects are usually resistant. Individuals who are of conservative, suspicious, or sceptical nature are not likely to profit from placebos. Such negative reactors, on the contrary, may become worse as per their 'own expectations'. A strong negative reactor may even take a pride in saying that he or she is "allergic to all drugs".

(c) *Form of administration* : It is not surprising that the greatest placebo effect (as high as 81%) is achieved with injections. Mixtures and pills are less effective. This may perhaps explain the current preference for the use of injections by the practitioners! Colour, taste, presence or absence of stress, are other factors which modify placebo effect.

Like active drugs, placebos can produce certain adverse subjective reactions, such as drowsiness, headache, dryness of mouth, fatigue, insomnia, constipation, impotence, difficulty in concentrating and a 'drugged feeling'. An abstinence syndrome, which responds to injection of saline, has been described after prolonged placebo therapy.

It must also be pointed out that much of the routine treatment such as vitamins, tranquillisers and tonics, prescribed by the doctors often acts as a placebo for themselves too! Many physicians cannot "bear to think they are doing nothing; so they, like their patients are willing to believe. They persuade themselves or are persuaded of the virtues of their treatment".

Interpretation of results : After the completion of the clinical trial the results are subjected to statistical analysis. If the difference between the two groups of treatment is so large that the probability of its occurrence simply by chance is less than 5 times in 100 ($p < 0.05$), then the new drug is said to have produced a significant effect. It is necessary, however, to rule out all other possible explanations for such difference, before the verdict is accepted.

Various statistical designs have been suggested to ensure that the results obtained are as precise as possible without much interference by other biological factors and individual bias; and there is no doubt that such statistical safeguards are essential. However, elaborate statistics cannot validate a poorly designed and executed clinical trial. Further, it should be realised that in a given study it is more important to know whether a new drug is significantly better than the older one or placebo in terms of its 'clinical effect' and not merely by the technique of the statistical analysis. In fact, an effect whose reality is revealed only after very elaborate statistics is hardly likely to be clinically important. 'Statistical significance' and 'Therapeutic significance' of results do not necessarily go hand in hand. Many times statistics would show 'a statistically significant difference', but it cannot tell whether such difference really

matters in therapeutics. Thus, a drug which lowers the plasma cholesterol concentration in a statistically significant way is not necessarily beneficial in the prevention of myocardial infarction.

Most of the new drugs are not 'wonder drugs' and need proper clinical assessment by controlled trials as outlined above. Unfortunately, because of various factors the quality of many so called trials is still far from satisfactory. As pointed out by the *Lancet*, there is no doubt that a prior design of the trial is important but "It is clearly not worth devoting such energy to trial design if the trained observer is not both trained and observing. After all, the controlled trial requires as much in 'clinical observation' as it does in design. No one should play at clinical trials". As pointed out by Parkhouse, "a good trial of a poor drug is a great deal better than no trial at all. It is infinitely better than a poor trial of a poor drug". Even the use of double blind technique does not guarantee valid results in an otherwise poorly designed and executed study.

DRUG PRESCRIBING

In practice, the treatment of a sick person includes many aspects, and administration of drugs is one of them. In certain patients drugs are of the greatest importance while in others they have only a minor role to play. It is important, therefore, that a practitioner who prescribes drugs should know:

- (1) Natural course of the disease he is treating.
- (2) Pharmacological actions and toxicity of a drug he uses.
- (3) Reasons for choosing a particular preparation, more so if it is a costly one.
- (4) Some methods of assessing the efficacy and toxicity of the drug/s used and
- (5) The possible interactions when several drugs are administered simultaneously.

In a country like India, the cost of the therapy is important. New drugs are invariably costly; however, many costly preparations sold in the market are neither new nor necessarily better than

older, established, -cheap preparations. In fact, established drugs are often introduced in the market under various trade names either alone or in various combinations and are sold at a fancy price purely with effective advertisement and modern sales promotion techniques. It should be remembered that real wonder drugs are rare and do not require much advertisement and an important principle of economics behind advertisement and sales promotion is to create a demand where real need does not exist. Drugs, therefore, should never be prescribed unless there is a definite indication for doing so and when they are used the benefit expected from them to the patient must outweigh the probable harm, immediate or remote, that could occur.

Whenever possible, drugs should be prescribed by their official names rather than by proprietary names.

Practitioners should always have a critical outlook towards accepting a new remedy. Many times drugs are marketed without adequate and reliable clinical trials and sometimes with excessive claims regarding their properties. An androgen is no doubt useful in the treatment of testicular deficiency due to organic disease or following castration. However, a sweeping recommendation for its prescription for all cases of the commonly encountered conditions like impotence or sterility is not justifiable. It is surprising that such remedies are extensively prescribed even though there is no reliable evidence of their value nor about their safety.

How you use a drug is more important than what drug you use. Proper use requires familiarity with both therapeutic and toxic responses. This is difficult if one switches from one preparation to another at frequent intervals. Usually, it is beneficial to be slow in accepting any new agent.

Adverse reactions to drugs are a serious hazard in modern medicine. It is unfortunate that doctors often over-prescribe drugs for trivial complaints. The reasons for this are not clear. Although this has some relation to increased demand by patients for drugs, the major fault

probably lies with the medical profession. Many busy practitioners find it difficult to keep in touch with the current literature and are easily persuaded by the promotional material from the pharmaceutical industry. Others probably would like to impress their patients by their 'most up-to-date' knowledge about 'the latest drugs', while some may not even bother about what preparation they prescribe and what drugs it contains nor are they aware of the various actions of those drugs.

The use of combinations of drugs is sometimes very useful and necessary but often it offers only a marginal advantage. Combinations of drugs would expose the patient to additional toxicity. Sometimes the combination may even reduce the effectiveness of therapy. Hence, combinations should be used only when indicated and each drug prescribed with a specific purpose. In such cases the doctor should combine the drugs himself rather than prescribing the ready made mixtures from the drug companies. This would give him an opportunity to regulate the doses of individual drugs as desired and would also reduce the cost of therapy.

A prescription should specify the drug, the total quantity and the form in which it is to be supplied. It should clearly indicate the dose, the frequency of administration, the duration of therapy and the manner in which the preparation is to be taken or applied. Paediatric preparations should be administered in palatable liquid form, preferably in syrupy base. The drugs prescribed should be the most suitable, the least costly, and easily available. It is not enough simply to note the failure of drug therapy and the adverse reactions produced. If one has to make any purposeful decision about the future use of the drug, it is necessary to know more about it. What is the cause of failure? How useful is the drug usually? Is it commonly used? For what condition is it usually given? What good does it do? Is the risk in its use worth the benefits expected? What other drugs are available? Can therapy be improved? This constitutes a *therapeutic audit* and would help the doctor in using drugs in future cases more

effectively and rationally.

Patient compliance : Except when hospitalized, patients are responsible for administering their own drugs. Very often, there is a gap between what is prescribed and what the patient actually takes. There are several, possible reasons for this: complexity of regimen (several drugs to be taken several times a day), cost, adverse effects, natural disinclination to take injections, poor motivation, length of treatment and so on. The drug regime should be as simple as it can be kept : as few drugs as possible and once or twice a day administration, if permissible. Cost being a major consideration in long-term treatment, only the cheapest drugs should be prescribed; this often means prescribing drugs by generic rather than by proprietary names. Patient's motivation may be improved by personal contact between him and either the physician or the clinic staff. A sympathetic discussion about the difficulties of drug administration and the possible adverse effects is likely to have a salutary effect on patient compliance. On the other hand, mere distribution of printed leaflets about drug administration, diet etc. may educate the patient but is less effective in improving patient compliance. Occasionally, it is necessary to take into confidence the patient's relatives, particularly in the case of old or psychotic subjects. Finally, occasional surprise check on plasma level of the drug or urinary excretion of its metabolites helps to detect defaulters but may be impracticable.

DRUG INTERACTIONS

Drug interactions result from the use of two or more drugs. This may lead to enhanced or diminished effect and may be useful or harmful. The useful drug interaction is illustrated by synergistic combinations of drugs such as antibiotics or antihypertensives (see Chapter 1). Harmful drug interactions are, unfortunately, more numerous and are discussed below.

A new symptom appearing during treatment with a drug may be due to the disease or the drug.

This can be perplexing enough. But, if the patient is receiving several drugs and two or more drugs are capable of causing the same new symptom as the underlying disease, or if two drugs in concert elicit symptoms that would not otherwise appear, the physician is in a quandary. In this situation, he may attribute the new symptom wrongly to the disease itself or to idiosyncrasy to one of the drugs, instead of recognizing it as a drug interaction. It is known that the incidence of adverse reactions to drugs rises from 4.2% when five or fewer drugs are used to 45% when twenty or more drugs are used. A physician who uses multiple drugs must, therefore, be constantly alert to the possibility of drug interaction. Further, he must be aware of both 'risky drugs' and 'vulnerable patients' in this respect. *Risky drugs:* This group includes (a) those that affect a vital process in the body e.g. warfarin, chlorpromazine and morphine; (b) those that have a steep dose-response curve e.g. verapamil, levodopa and chlorpropamide; (c) those that have saturable kinetics e.g. phenytoin, theophylline and alcohol; (d) those that demonstrate concentration dependent toxicity e.g. digoxin, lithium, aminoglycosides and methotrexate; (e) those where a loss of effect leads to breakthrough of the disease e.g. quinidine, glucocorticoids and antiepileptics; and (f) those where the patient depends on prophylactic action e.g. oral contraceptives and cyclosporin. *Patients particularly vulnerable to drug interactions are:* (a) elderly patients receiving many drugs; (b) acutely ill patients; (c) patients with unstable disease e.g. epileptics, brittle diabetics, demented patients and those with cardiac arrhythmias; (d) patients dependent on drug treatment e.g. transplant recipients and patients with Addison's disease; and (e) patients who have more than one prescribing doctor. It is absolutely essential that when a patient's clinical condition changes, particularly if he is severely ill or elderly, all drug treatment should be reviewed as a matter of course.

Drug interactions may occur either outside the body or in the body.

I. Drug interactions outside the body:

The most glaring examples of this are seen when several drugs are mixed in an intravenous drip. One or more of the drugs may get inactivated or even precipitated. This is often attributable to changes in the pH of the solutions. The following are some of the examples of the incompatibilities of drugs in an intravenous drip.

(a) *Use of a wrong vehicle for infusion:* No drug should ever be added to blood, plasma, amino acid solutions, fat emulsions (which tend to crack), sodium bicarbonate solution and mannitol solution (from which mannitol tends to crystallize).

Highly acidic solutions (pH may be as low as 3.5) such as dextrose, levulose or fructose are unsuitable as vehicles for sodium or potassium salts of weakly acidic drugs such as sulfonamides, barbiturates, methicillin and novobiocin, as the latter tend to get precipitated at this pH. Drugs such as benzyl penicillin, ampicillin, heparin and aminophylline are unstable at the pH of these solutions. Dextrose solution is, however, eminently suitable for infusing noradrenaline which

is stable at the acidic pH.

Isotonic saline is slightly acidic or neutral and is a suitable vehicle for most drugs with the exception of noradrenaline which is unstable at this pH. If noradrenaline has to be infused in isotonic saline, vitamin C should be added to the drip to ensure its stability.

Most antibiotics become unstable and deteriorate in large volumes of fluid. Moreover, erythromycin lactobionate is unstable in electrolyte solutions but may be diluted with 5% dextrose solution. Amphotericin B should be diluted with 5% dextrose solution of a pH recommended by the manufacturer.

(b) *Mixture of drugs in an infusion :* Barbiturates, phenytoin, phenothiazines, vitamin B complex (\pm vitamin C), amphotericin, sulphadimidine, sulphadiazine and furosemide should not be mixed with any other drug in solution.

The other examples of incompatibilities in infusions are given in Table 2.1.

II. Drug interactions in the body : These have either *pharmacokinetic basis*, one drug af-

Table 2.1 : Drug incompatibilities in intravenous fluids

Drug	Incompatible with	Reason
The Penicillins	Tetracyclines (HCl) Gentamicin	Precipitation Inactivation of Gentamicin
Carbenicillin	Kanamycin Colistin Gentamicin	Inactivation of Carbenicillin Inactivation of Colistin Inactivation of Gentamicin
Tetracyclines (HCl)	Penicillin Sulfonamide (Na^+ salts) Hydrocortisone Sodium Succinate Calcium Salts Cephaloridine Sodium Bicarbonate	Precipitation Precipitation Precipitation Tetracycline chelate formed Precipitation Precipitation
Heparin Sodium	Hydrocortisone Sodium Succinate Sympathomimetic amines Tetracyclines Aminoglycoside Antibiotics (Gentamicin, Kanamycin, Streptomycin)	Precipitation Precipitation Precipitation Precipitation

fects the absorption, metabolism or excretion of another drug, or *pharmacodynamic basis* i.e. one drug alters the receptor activity of another drug.

(I) Absorption:

(i) Some drugs given orally interact in the gastrointestinal tract to form complexes which may not be absorbed. Thus, calcium, magnesium, aluminium and iron salts can interfere with absorption of antibiotic tetracycline and of prednisolone. Sucralfate reduces the bioavailability of phenytoin. The impairment of oral absorption of the anticoagulant warfarin by cholestyramine-resin is probably of similar nature. These interactions can be avoided by separating the administration of the two drugs by at least two hours.

(ii) A drug altering the gastric pH can alter the solubility of another agent and thus may influence its absorption e.g. sodium bicarbonate reduces the absorption of tetracycline. Drugs can also affect the absorption by modifying the gastrointestinal motility and gastric emptying. Thus, anticholinergic drugs and opioids can slow down the absorption of other drugs by delaying gastric emptying.

(iii) Sorbitol accelerates the gastrointestinal absorption of paracetamol, and vitamin C in large doses accelerates the absorption of iron.

(iv) A few women taking low dose combination oral contraceptives may be put to risk of pregnancy by the concurrent administration of a broad spectrum antibiotic (ampicillin or tetracycline but not co-trimoxazole). By reducing the bacterial flora in the intestines, these antibiotics disrupt the deconjugation and hence re-absorption of the steroids secreted into the intestine.

(2) **Drug distribution:** Some drugs are bound strongly to plasma proteins and in this state, are pharmacologically inactive. Certain groups of drugs seem to share a limited number of protein binding sites and can be displaced from them by each other. This results in an increase in the unbound and pharmacologically active form of one of the drugs leading to toxicity. However, this type of drug interaction is clinically significant only with drugs which have a small apparent volume of distribution (V_d). Thus,

(i) Phenylbutazone, oxyphenbutazone and clofibrate can displace warfarin sodium from the binding sites, leading to a bleeding tendency.

(ii) Salicylates and sulfaphenazole can displace tolbutamide from the binding sites, leading to hypoglycemic coma.

(iii) Sulfonamides and salicylates can displace methotrexate from protein binding.

(iv) Sulfaphenazole, sulfamethoxypyridazine and salicylates can displace bile pigments from the binding protein, particularly in neonates, causing kernicterus.

(3) **Drug transport:** Guanethidine and the related adrenergic neurone blocking drugs are actively transported into adrenergic neurons by the same transport system that is responsible for the noradrenaline uptake into the neurone. This system is inhibited by the antidepressant imipramine, which therefore, also interferes with the antihypertensive activity of guanethidine.

(4) Drug metabolism:

(a) *Stimulation* : The activity of the drug metabolizing microsomal enzymes is increased by a number of commonly used drugs, insecticides and polycyclic hydrocarbons. This phenomenon increases the therapeutic dose of the inducing agent as well as of those drugs metabolized by the microsomal enzymes. A few important examples are,

(i) Rifampicin accelerates the metabolic degradation of glucocorticoids and oral contraceptive pills, and diminishes their efficacy.

(ii) Phenytoin and phenobarbitone are known to induce vitamin D deficiency by accelerating its wasteful degradation in the liver.

(iii) Chloral hydrate and barbiturates such as phenobarbitone enhance the hydroxylation of coumarin anticoagulants. Serious and fatal haemorrhage has been reported after the withdrawal of chloral hydrate and phenobarbitone in patients on oral anticoagulants.

(iv) Phenobarbitone stimulates the metabolism of phenytoin and griseofulvin.

(v) The chlorinated hydrocarbon insecticides

dicophane (D.D.T.) and gamma benzene hexachloride enhance the rate of metabolism of antipyrine. These insecticides are powerful enzyme inducers in laboratory animals and hence, research into drug effects could be grossly misleading if the animal quarters are sprayed with these insecticides.

(b) *Inhibition* : The inhibition of drug metabolism has become increasingly important with the numerous cases of drug toxicity attributed to it. Thus,

(i) Tolbutamide metabolism is depressed by disulfiram and chloramphenicol and a dangerous hypoglycemia may result if any of these drugs is administered along with tolbutamide.

(ii) The p-hydroxylation of phenytoin is inhibited by dicoumarol, isoniazid, sulfaphenazole, p-aminosalicylic acid, disulfiram, sulthiame, chloramphenicol and methylphenidate. The latter is also reported to inhibit the metabolism of primidone, phenobarbitone and ethylbiscoumacetate.

(iii) Allopurinol inhibits the metabolism of 6 mercaptopurine, leading to bone marrow toxicity.

(iv) The metabolism of alcohol is interfered with by disulfiram and chlorpropamide producing flushing, diarrhoea and hypotension.

(5) *Receptor site*: In this case, drugs acting on the same receptor site or at different active receptors may enhance or decrease the response e.g. d-tubocurarine and aminoglycoside antibiotics may accentuate the block at the neuromuscular junction; marked CNS depression is caused by combined administration of morphine and barbiturates. Examples of pharmacodynamic drug interactions are many and are described in respective chapters.

(6) *Drug excretion*: This can be facilitated or interfered with by certain drug combinations. Thus, the excretion of weakly acidic drugs like sulfonamides, salicylates and barbiturates can be enhanced by making the urine alkaline. The weakly alkaline drugs like the ganglion blocking agents are better excreted in an acidic medium. Phenylbutazone interferes with the tubular secretion of penicillin, and of hydroxyhexamide, an

active metabolite of acetoexamide. Probenecid inhibits the tubular secretion of penicillin, indomethacin and riboflavine. Quinidine, verapamil and amiodarone can all as much as double the plasma concentration of digoxin.

(7) *Changes in electrolyte and fluid balance*: Drugs that cause potassium depletion may potentiate the effects of digitalis and non-polarizing muscle relaxants, but antagonize the anti-arrhythmic action of lignocaine, quinidine and procainamide.

(8) *Interactions among chemotherapeutic agents*: Injudicious combinations of chemotherapeutic agents may prove harmful in therapeutics. This is discussed in detail in Chapter 46.

Unfortunately, such interactions are not always predictable from animal studies. Hence, the physician should always be wary about including too many drugs in his prescription so as to minimize this danger. Further, the physician should always enquire about alcohol consumption by the patient. Many people consume alcohol in varying amounts either for medicinal purposes or socially. Numerous drug interactions between alcohol and other drugs have been reported. Thus, drugs known to cause CNS depression such as analgesics, hypnotics, tranquilizers, anti-histaminics, anticonvulsants, reserpine, methyldopa and clonidine may cause severe CNS depression when consumed concomitantly with alcohol. Additive orthostatic hypotension can occur from the use of alcohol and vasodilator drugs like hydralazine and nitroglycerine. On the other hand, heavy consumption of alcohol is known to cause transient hypertension. Potentially severe reactions can occur when alcohol is consumed concomitantly with aspirin, antidiabetic sulfonylureas or oral anticoagulants. Finally, it should be remembered that chronic alcoholics may metabolize certain drugs faster because of increase in metabolizing activity of hepatic microsomal enzymes. Thus, isoniazid, an anti-tuberculosis drug, may cause hepatic toxicity in alcoholics because of increased production of a toxic metabolite (See

Chapter 4).

Many of the drug interactions reported in the literature (especially those which are due to competitive binding to the same plasma protein) may not be clinically significant. Therefore, one should be careful in distinguishing between drug interactions which are clinically significant and those which are not.

Limited prescribing lists : This concept has been advocated for use in hospitals and has sev-

eral advantages. (1) It would improve the practitioner's knowledge of the drugs he is prescribing and hence the quality of prescribing. (2) It would reduce the cost of patient care: Based on certain criteria, the W.H.O. has prepared a model list of essential drugs. It contains about 220 essential drugs and vaccines needed for good medical practice. More than 80 developing countries have developed such model lists to suit their own requirements.

Section II : Drugs Acting on The Central Nervous System

3 General Considerations

Anatomically, the nervous system in higher animals can be divided into (a) the central nervous system (CNS) and (b) the peripheral nervous system consisting of somatic and autonomic nerve fibres. The central nervous system is not only concerned with the regulation of specialized functions like circulation, digestion and respiration but it also modifies the psychic reactions such as feeling, attitude, thoughts and memory. The ability to think logically, to learn from past experiences and to communicate appropriately are the unique qualities of man which can be attributed to the development of the highly specialized central nervous system.

Both the CNS and autonomic nervous system can be considered as analogous to an elaborate system of telegraphy wherein numerous wire connections in the form of neurons bring in information from both internal and external environment. This information is received, 'decoded', decisions are made by various centres in CNS and instructions are sent out to various peripheral tissues to produce appropriate responses. The reaction pattern could be psychic as manifested by change in emotions, thought and attitude. It could be somatic, as demonstrated by various types of body movements or autonomic, as indicated by changes in respiration, circulation and visceral functions.

The major anatomical divisions of the CNS are the cerebrum, the cerebellum, the brain stem and the spinal cord. Functionally, it consists of billions of neurons organized to form several neuronal systems with nuclei and their tracts, each concerned with certain specialized functions such as motor activity, perception and regulation of

various body functions. These systems, however, are essentially interdependent and a disturbance in one may produce repercussions in other systems as well. It is also likely that one area may modify or control more than one function.

The limbic system consists of the hippocampus, the amygdaloid complex, the septum, the hypothalamus, the olfactory and pyriform lobes, the basal ganglia, and a part of the thalamus; this is also sometimes called the visceral brain.

When the central nervous system is exposed to the action of depressant drugs, the recently acquired or phylogenetically newer functions such as fine control of movements, association and memory are the first to be affected as compared to those controlling respiration and circulation which are primitive and basic. The depression thus starts from the cortex and proceeding through the diencephalon, the midbrain and the spinal cord, affects the vital medullary centres last. This irregularly descending paralysis is a built-in safety mechanism which tries to conserve the functions essential for life at the cost of more sophisticated and dispensable functions. The recovery from the depressant effect occurs in the reverse order.

The knowledge about the physiological functions of various areas of the CNS is far from adequate. Most of the higher functions of the CNS cannot be explained in physiological terms. More is known about what the brain does than about how it does it. Consequently, information regarding how the drugs modify its functions is still inadequate. The physiological functions attributed to various parts of CNS are given in Table 3.1.

Table 3.1 : Functions of various parts of central nervous system

Part of CNS	Functions attributed
Cerebral cortex	Higher functions like judgement, memory, fine voluntary movements, fine pain, tactile discrimination and temperature, special senses like vision, smell and hearing. It also acts as an important coordinator and exerts inhibitory control over lower centres.
Frontal lobes	Thinking, integration of emotional behaviour.
Limbic system	Integrates emotional state with motor and visceral activities.
Basal ganglia	Extrapyramidal control of skeletal muscle tone, co-ordination of posture. Lesions produce tremors and rigidity in flexion.
Thalamus	Relay centre for sensory pathways to cortex. Conscious appreciation of pain, temperature and crude touch sensations. Exerts regulatory control over visceral functions.
Hypothalamus	Control of the autonomic nervous system, control of adenohypophysis. Important centre of integration of eating, drinking, sexual behaviour, temperature regulation, sleep and other vegetative functions.
Cerebellum	Control of vestibular function and body posture.
Reticular formation	Sleep-wakefulness cycle, control of blood pressure, respiration, swallowing, vomiting; transmission of crude pain, voluntary muscle tone and posture; control of upper motor neurons.
Spinal cord	Reflex movements, control of muscle tone (particularly the red muscles) and the upper and the lower motor neurons through presynaptic and post-synaptic inhibition.

It must be emphasised that there is no absolute control of a particular function vested in a given area of the central nervous system and the ultimate modulation of a function is the result of interaction between several synergistic and antagonistic components. Further, most experimental evidence regarding brain function is derived from lower animals in whom the brain is obviously different from that in man.

The reticular formation is a heterogenous mass of cell bodies enmeshed in a network of dendrites and axons located in the central core of the medulla, pons and midbrain. It includes all the gray matter in these areas except that belonging to cranial nerve nuclei, cerebellar relay nuclei and lemniscal relay nuclei. Caudally it is continuous with the spinal gray matter while rostrally it disappears into subcortical nuclei, particularly of the thalamus. It is thus a diffuse multisynaptic system.

A complex, interrelated group of pathways coursing through the reticular formation of the midbrain and medulla and extending rostrally into the thalamus and the hypothalamus have been termed as '*reticular activating system*'. All the sensory information courses through the reticular formation. The latter arouses the cerebral cortex. It is essential for the regulation of sleep and wakefulness and for coordination of gaze and eye movements.

The reticular formation is considered to be intimately concerned with transmission of crude pain and other sensations, state of consciousness, control of muscle tone and posture and such vital functions as respiration and circulation.

Drugs can affect the central nervous system in the following ways:

(a) They may act directly on neurons and modify the neuronal functions.

(b) They may act reflexly by sending afferent impulses to the central nervous system via the chemoreceptors, baroreceptors and peripheral nerves and thereby eliciting psychic, somatic or visceral responses.

(c) They may affect the nutrition and oxygen

supply of the CNS by altering its blood supply or affecting its metabolism e.g. by causing hypoglycemia or ammonia intoxication.

To reach the central nervous system, a drug must have a high degree of lipid solubility (high oil/water partition coefficient) or a specialized transport mechanism. Ionized drugs as a rule cannot penetrate into the central nervous system. For this reason the existence of a 'bloodbrain barrier' has been postulated.

The condition of the meninges, however, can alter to a certain extent the penetrability of drugs in the central nervous system. Thus, in the presence of meningeal inflammation (meningitis) considerable amount of penicillin can cross the blood-brain barrier, which is not so in a healthy individual.

Types of drug action: Drugs may either stimulate or depress the central nervous system. Excessive stimulation of the CNS may produce convulsions, which could be of cortical, medullary or spinal in origin. In therapeutic doses the stimulant action is usually selective (confined to specific areas of the CNS) whereas in toxic doses convulsions may be produced.

Suppression of inhibitory areas in the central nervous system may result in an apparent stimulation. Thus, ethyl alcohol eliminates the inhibitory control exerted by the higher cortical centres and leads to garrulousness and hilarity.

Excessive stimulation of the CNS is followed by its depression and even by permanent loss of its functions.

Depression or inhibition of the CNS may be achieved through more than one mechanism. Like the peripheral nervous system the central nervous system is postulated to contain a number of inhibitory and excitatory chemical transmitters. Inhibition achieved as a result of hyperpolarization of the postsynaptic membrane by the active release of an inhibitory transmitter is termed the *postsynaptic* inhibition, while inhibition achieved by reduction in the quantum of the excitatory transmitter released in the synaptic cleft is termed *presynaptic* inhibition. A well-known example of

postsynaptic inhibition is that exerted by the Renshaw cells of the spinal cord on the lower motor neurons. Renshaw cells are postulated to exert this inhibitory control by the release of an inhibitory neurohumoral transmitter.

Depression could be *non-selective* (general) or *selective* (localized), restricted to certain areas within the central nervous system. Thus, depressants like general anaesthetics and hypnotics are non-selective in action, while drugs like phenytoin sodium and chlorpromazine produce more selective actions. However, a specific depressant may produce unusual excitation under certain circumstances. Thus, barbiturates may induce anxiety and apprehension when employed in the presence of pain, and tranquillizers like chlorpromazine may unmask epilepsy.

The action of the selective central nervous system depressants may also be modified by the internal environment; the amount of a general anaesthetic required to anaesthetize a highly excited subject is more than that required in a normal person. Although selectivity of action may be remarkable, a drug normally affects several CNS functions to varying degrees, which could cause unwanted side effects.

Neurochemical transmitters in the central nervous system: It is now generally accepted that transmission at most, if not all, synapses in the mammalian CNS is mediated by chemical agents called neurochemical (neurohumoral) transmitters. A substance must satisfy certain criteria in order to be accepted as a neurohumoral transmitter. Thus,

(a) The substance claimed to be a transmitter must be present in the nerve endings and should have a discrete rather than a uniform pattern of distribution.

(b) The substance must be elaborated within neurons and released from the presynaptic nerve terminals.

(c) Local concentration of the substance should be related to the function of the neuronal structure, and fluctuations in its concentration should take place in response to functional

changes in the neuron.

(d) Enzymatic mechanisms capable of synthesising and destroying the substance should be present within the neurons. Such mechanisms should essentially have a high velocity, in order to correspond with the rapidity of events occurring in the central nervous system.

(e) Clearly demonstrable effects should be obtained by increasing or decreasing the local concentration of such substance in the central nervous system. When applied to the post-synaptic cell body, the substance should mimic the action of the synaptically released chemical transmitter.

(f) Known blocking agents of this substance should produce demonstrable effects by preventing the access of the transmitter to specific receptor sites.

It is now generally accepted that the CNS has excitatory and inhibitory chemical transmitters. Some of the probable transmitters are given in Table 3.2. Of these dopamine, GABA and glycine have been considered as inhibitory transmitter substances. However, all of these do not satisfy all the criteria mentioned above. It is, however, interesting to note that many drugs which modify the functions of the CNS have been demonstrated to affect the concentration of one or more of these substances in the central as well as peripheral nervous system. The bodies of the nerve cells in the CNS are densely covered by synapses and it is probable that they have more than one transmitting substance acting on their surface.

Apart from the neurochemicals mentioned in Table 3.2, several endogenous peptides have been

Table 3.2 : Various neurochemicals detected in the central nervous system

Name	Distribution	Effects
Acetylcholine	Widely distributed in almost all regions of CNS. Predominantly in cerebral cortex, ascending reticular system, cerebellum and spinal cord.	Both excitatory and inhibitory in nature. Central effects can be blocked by atropine.
Noradrenaline	High concentration in the hypothalamus, limbic system and reticular formation in the brain stem.	Both excitation and inhibition in the brain stem.
Dopamine	Mainly in the basal ganglia, to some extent in the hypothalamus, adenohypophysis and frontal cortex.	Predominantly inhibitory action. Deficiency causes extrapyramidal disturbances.
5-Hydroxytryptamine	Similar to noradrenaline. Extends into the cerebral cortex and hippocampal areas.	Both excitatory and inhibitory effects.
Histamine	Distribution similar to noradrenaline and 5-HT but irregular.	Mainly inhibitory effects. Functions uncertain.
L-glutamic acid and related amino acids.	Widely distributed	Excitant effects.
Gamma-aminobutyric acid (GABA), glycine	GABA in CNS; glycine mainly in the spinal cord and brain stem.	Inhibitory effects in brain and the spinal cord.
Substance P	Hypothalamus, thalamus, basal ganglia and in the dorsal column and roots of the spinal cord.	
Prostaglandins(?)	Not yet well defined, cerebral cortex.	Excitant and inhibitory effects.

discovered in the brain. These include enkephalin, endorphines, endocrine peptides (somatostatin, TRH and LHRH) and even gut peptides (gastrin and cholecystokinin).

Basis of drug action :

(a) Drugs may modify the synthesis, storage, release or metabolism of the inhibitory or excitatory neurochemical transmitters. Thus, monoamine oxidase inhibitors act as antidepressants by inhibiting the destruction of noradrenaline by the enzyme monoamine oxidase. The transmitter-dependent actions of drugs can be conveniently classified into pre-synaptic and post-synaptic.

(b) Drugs may modify the energy supply of the central nervous system. This may be achieved by local inhibition of the synthesis of high energy phosphate bonds (barbiturates), by inhibition of action of certain enzymes involved in cellular respiration and energy processes or by increasing or decreasing the availability of the substrate for energy production.

(c) Drugs may act by modifying ionic fluxes across the cell membrane e.g. phenytoin sodium.

(d) Drugs may specifically act as antagonists of other drugs at receptor levels, e.g. antagonism of morphine by nalorphine.

Under certain circumstances, the central and the peripheral effects of a drug may be antagonistic. Atropine in small doses stimulates the central vagal nucleus and induces bradycardia while the therapeutic doses usually induce tachycardia by peripheral cholinergic blockade.

Methods of investigation : The experimental procedures employed to study actions of drugs on

the central nervous system have advanced from relatively simple techniques like intracarotid and intravertebral administration of drugs in anaesthetized animals to implantation of drug pellets in specific areas of the central nervous system and microiontophoresis. The properties of cellular response to drugs can be studied electrophysiologically by the use of a technique involving recordings from a single cell and highly localized drug administration (Microiontophoresis).

A broad screening programme in a laboratory working on CNS pharmacology consists of scores of experiments where initially, overall drug effects like stimulation and depression are investigated in small animals. The tests used for this purpose include the effect of drugs on consciousness and righting reflex and their effect on the motor response as gauged by the patellar reflex. It is, however, important to note that a variety of drugs may evoke a similar response with a particular test. For example, all the CNS depressants are capable of producing a loss of righting reflex, when administered in a sufficiently large dose, and such a loss can also be produced by the peripherally acting skeletal muscle relaxants like d-tubocurarine. Following these preliminary investigations, specialized properties like analgesic, hypnotic and anticonvulsant effects are studied with the help of more sophisticated techniques. However, in many cases, the complexity of the system and lack of experimental analogy to human pathological conditions preclude clear conclusions. Certain latitude, therefore, must be allowed for critical correction of current concepts, even those which at the moment may appear quite adequate and sound.

4 Aliphatic Alcohols

Aliphatic alcohols are hydroxy (OH) derivatives of the aliphatic hydrocarbons. They may contain one, two or more OH groups and are designated as

(a) Monohydroxy e.g. ethyl, methyl, propyl alcohols

(b) Dihydroxy, also called as glycols due to the sweet taste, e.g. ethylene glycol, propylene glycol

(c) Trihydroxy, e.g. glycerol or glycerine.

(d) Polyhydroxy e.g. mannitol, sorbitol

Only ethyl alcohol is commonly consumed by humans. Glycerol is formed during the digestion of fat.

ETHYL ALCOHOL: This is the main constituent of all kinds of alcoholic beverages and is generally obtained by fermentation of sugar by yeast. The alcohol is separated by simple distillation. It is a colourless, volatile and inflammable liquid. Neutral spirit contains 90-95% alcohol by volume. Wines containing more than 16% of alcohol are prepared by fortifying by the addition of neutral spirit. The alcohol content of various beverages varies between 4-55% by volume. Stronger preparations are called spirits.

Pharmacological actions: Local actions depend on the concentration of alcohol and the tissue to which it is applied. Because it evaporates quickly from the skin, it has a cooling and refreshing effect and is used for reducing the temperature in fevers. In concentrations of 40-50% it has a rubefacient and mild irritant action. Higher concentrations denature proteins by partial precipitation and dehydration; in such concentrations it acts as an astringent, a germicidal and an irritant. Concentrated alcohol, if injected, produces tissue destruction. Alcohol in a concentration of 70% by weight acts as an antiseptic; the action is seen only

against vegetative forms of organisms; spores are resistant.

Gastrointestinal tract : Taken orally, it gives a local feeling of warmth and increases the salivary secretion probably by reflex action. It has an irritant action on the gastric mucous membrane and enjoys reputation as an appetizer; 50 ml. of 7-10% alcohol increases the gastric secretion, probably by releasing histamine and gastrin from the antrum of the stomach, in addition to its psychic and local irritant effects. Concentrations above 15% inhibit both motility and secretion and this effect may persist for many hours. Higher concentrations produce marked irritation of the mucous membrane and may precipitate gastritis, giving rise to nausea, vomiting and other symptoms. Concentrations above 20% reduce the enzymatic activity of the gastric and the intestinal juices. Many chronic alcoholics suffer from gastritis and achlorhydria. *The irritant effect of alcohol on the gastric mucosa is accentuated by aspirin.*

Central nervous system : It depresses the central nervous system in a descending order. In small doses it causes euphoria, freedom from anxiety and worry and may improve social communication; this effect is the chief reason for the popularity it enjoys. This action may be beneficial therapeutically by relieving pathological nervous tension and by improving appetite in anorexia.

Normally, man exercises inhibitions in order to live a disciplined life as desired by the society. Alcohol removes these inhibitions and thus diminishes such characteristics as hesitation, caution and self-criticism. The pattern of behaviour then depends on the environment and the basic personality of the individual. Under the influence

of alcohol, mood swings and uncontrolled emotional outbursts are common; the individual may do silly and harmless antics but sometimes he can become vicious and anti-social, or reckless. Alcohol is thus incriminated in one out of five crimes of violence.

This initial effect is due to a depression of the reticular activating system. The cortex is thus released from the integrating control or inhibitions required for purposeful activity.

Alcohol reduces visual acuity and interferes with muscular co-ordination even in small doses that do not produce gross intoxication. It impairs the ability of the brain to co-ordinate muscular activity such as typing, standing and hand steadiness. It lengthens the reaction time for both visual and auditory stimuli; in a mildly intoxicated person the reaction time may be lengthened by 10-15 per cent. Hence, even moderate drinking is considered dangerous to public and individual safety. This is more so if the individual is already taking some other central nervous system depressants like sedatives, tranquillizers or analgesics.

Following the ingestion of 60 ml. of 95 per cent alcohol, the pain threshold is raised by 35-40 per cent. Although it is not an analgesic, it alters the patient's reaction to pain from one of concern to one of relative detachment.

With increasing quantities, the individual loses all sense of proportion. Difficulty in speech, unsteadiness of gait and complete loss of self control are likely to follow. Large quantities of alcohol ultimately depress the CNS sufficiently to cause unconsciousness. The respiration becomes slow and stertorous, the face becomes pale and cyanotic and the blood pressure falls. Death occurs due to depression of the vital medullary centres, mainly the respiratory centre. Some of the CNS effects of alcoholic beverages consumed in large quantities are probably due to substances (ethyl acetate, isoamyl alcohol and butanol) other than ethanol present in these beverages. In epileptics, alcohol may cause convulsions.

Cardiovascular system : Alcohol in moderate amounts causes dilatation of skin vessels by

a central action resulting in flushing and feeling of warmth. This effect prevents normal cutaneous vasoconstriction on exposure to cold. Hence, it may be harmful to take alcohol for warming up in cold weather as the body would lose more heat through the dilated skin vessels.

Taken in concentrated form (Brandy 30-50 ml.) alcohol probably stimulates reflexly the vital medullary centres by irritating the pharyngeal mucosa, resulting in a slight rise in blood pressure, acceleration of the heart and an increase in the cardiac output; the effect is transient. For this reason it is used as a household remedy for fainting attacks.

Usefulness of alcohol as a coronary dilator is doubtful. It may relieve anginal pain but the effect is probably due to central action and not due to the dilatation of coronaries. In fact, the euphoria produced by alcohol may give a false sense of well being with a tendency to ignore the warning symptoms since alcohol is known to modify the attitude of the individual towards pain. In large doses alcohol depresses the heart like chloroform or ether. Habitual heavy spirit drinking over many years causes direct injury to the heart muscle and the condition known as 'alcoholic myocardiopathy' is now an established entity. Since even a small amount of alcohol has been shown to depress the myocardial function in patients with coronary or valvular heart disease, prescription of alcohol to patients with these diseases as a 'tonic' or as a 'coronary dilator' is irrational and unwise. Chronic alcohol ingestion is suspected to increase the risk of developing hypertension.

Liver : In the liver, alcohol brings about impaired gluconeogenesis, reduced synthesis of albumen and transferrin, increased synthesis of lipoproteins (with consequent increase in serum triglycerides) and decreased fatty acid oxidation.

Acute alcohol ingestion *inhibits* the hepatic microsomal enzyme systems whereas chronic alcohol ingestion *stimulates* them with resultant increase in the rate of metabolism of many drugs and of alcohol itself. The effect of enzyme induc-

tion can be offset by liver damage induced by alcohol and/or nutritional deficiency.

Clinically, hypoglycemia and hepatomegaly are the two important manifestations. Hypoglycemia is liable to occur in people who ingest large quantities of alcohol but eat poorly, particularly if they are on insulin or sulfonylurea drugs as in the treatment of diabetes. Hepatomegaly may be due to one of the several causes: simple hepatomegaly (with normal hepatic structure), fatty degeneration, alcoholic hepatitis, cirrhosis or hepatoma. Alcoholic damage is a direct effect of alcohol on the liver and it is doubtful if a high protein diet protects the liver from the ravages of alcohol. However, it takes many years of heavy drinking to produce cirrhosis. Women seem to be more susceptible than men and there appears to be some genetic predisposition based on HLA phenotype.

Kidney : Alcohol ingestion is known to increase the output of urine. This is probably due to decreased tubular reabsorption of water following depressed A.D.H. production. It also increases the excretion of magnesium and calcium, and decreases that of potassium.

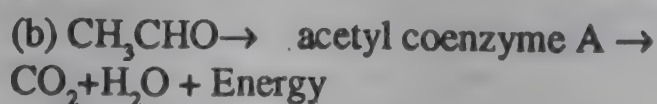
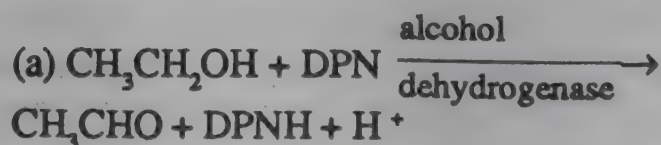
Other effects : Alcohol has an erroneous reputation as a sexual stimulant (aphrodisiac effect). The feeling of false confidence produced by the loss of inhibitory control is probably responsible for the tendency toward sexual excess observed in intoxication. But as Shakespeare correctly noted in 'Macbeth', "Lechery, Sir, it provoketh and unprovoketh; it provoketh the desire, but it taketh away the preformance". In fact, it significantly depresses the sexual responsiveness in men and women. Further, in men, chronic alcohol ingestion is known to lead to reduction in plasma testosterone levels, impotence, sterility and gynecomastia. It may also produce prostatic congestion causing acute urinary retention. Large doses of alcohol damage the muscle, causing alcoholic myopathy. By stimulating ACTH secretion, chronic ingestion of large doses of alcohol has been shown to lead to 'pseudo Cushing's syndrome'. Drinking during pregnancy can have damaging effects on the fetus. The fetus has been

described to have "characteristic facial appearance, prenatal onset of growth retardation, mental deficiency and an increase in the frequency of major abnormalities" (*the foetal alcohol syndrome*). Even moderate alcohol consumption during pregnancy increases the risk of spontaneous abortion and low birth weight.

Absorption, fate and excretion: Ethyl alcohol is absorbed as such very rapidly from the stomach, duodenum and jejunum. It passes rapidly through various body membranes and finally gets distributed throughout the body water. Almost half the ingested quantity is absorbed within 15 minutes and the absorption is complete within 1-2 hours. The absorption is delayed by the presence of food in the stomach. It is stored in every tissue and diffuses back into the blood when blood level falls.

In the lung alcohol passes from blood to breath, which smells of alcohol. The ratio of concentrations of alcohol in blood and alveolar air is constant and is about 2,100:1. Because of this high ratio it is difficult to wash out blood alcohol by artificial ventilation in case of acute alcohol poisoning.

Over 90 to 98 per cent of alcohol is metabolized in the body, mainly by the non-microsomal enzymes in the liver. The rest is excreted by the kidney and lungs. Alcohol is first oxidized to acetaldehyde in the liver. Acetaldehyde is converted to acetyl coenzyme A and finally oxidized to carbon dioxide and water by liver as well as other tissues.



Alcohol is metabolised at a constant rate which is independent of blood alcohol concentration but is proportional to the body weight and probably to liver weight; thus an average individual can metabolise about 10 ml. of absolute alcohol in one

hour. There is no known method by which one can enhance the metabolism of alcohol. However, because of enzyme induction, this rate is often increased in alcoholics who have been drinking recently.

Is alcohol a food ? One gramme of alcohol gives 7.1 calories. Alcohol gives calories only in the form of acetate. Although it can spare carbohydrates and proteins, alcohol cannot act as a complete food, because the calories available from its hourly oxidation are inadequate even for maintenance of basal metabolism. In fact, the chronic alcoholics suffer from various dietary deficiencies.

Therapeutic uses of ethyl alcohol: It is a solvent for various alcohol soluble active ingredients. Therapeutically alcohol has few uses. It is sometimes used :

(1) in the symptomatic treatment of fever because of its cooling effect on skin,

(2) in the prevention of bed sores as it hardens the skin,

(3) as an antiseptic in the concentration of 70 percent by weight,

(4) to wash out phenol in cases of accidental skin contamination,

(5) as an appetizer (10%) and a carminative, and

(6) to destroy a nerve as in trigeminal neuralgia.

Acute alcoholism : Chemical analysis of blood and urine can give some idea about the degree of intoxication in an individual who has

ingested alcohol. (Table 4.1). However, it is difficult to associate a particular blood alcohol concentration with a specific degree of impairment. Blood alcohol concentration in excess of 80 mg % greatly increases the risk of driving accidents.

After death the detoxification of alcohol ceases and the brain and blood levels of alcohol remain constant for sometime. Hence, post-mortem samples of blood can give reliable estimates about the degree of intoxication at the time of death. Approximately 600 ml. of pure alcohol can produce a fatal effect in an individual of 70 kg. body weight. Coma in an acute alcoholic bout may be due to the CNS depressant effect of alcohol, head injury or severe hypoglycemia which is especially likely to occur in fasting individuals.

The treatment consists of general nursing care, maintenance of vital functions, reduction of cerebral edema by using mannitol, intravenous administration of glucose to combat hypoglycemia which is common and large I.V. doses (100 mg) of thiamine. Death due to acute alcohol poisoning, however, is uncommon.

If the acutely intoxicated patient is not comatose but only rowdy, careful use of a sedative is indicated.

Chronic alcoholism: Although all those who drink alcohol are not addicts, repeated ingestion of alcohol can lead to addiction. In addicts, the normal feeling of well being depends on a con-

Table 4.1 : Correlation of blood levels of alcohol with behavioural changes

Blood concentration mg. per 100 ml.	Behavioural changes	Interpretation
<50	Not significant	Not under the influence of alcohol
50-100	Feeling of exaltation, talkativeness	Possibly under the influence
100-200	Emotionally unstable, motor incoordination, nystagmus	Probably under the influence
200-300	Staggering, loss of self control	Definitely under the influence
300-400	Stupor— dead drunk	Grossly intoxicated
400-500	Coma, anaesthetic effect	
>500	Respiratory arrest and death	

tinuous availability of the drug molecules in the body fluids and tissues, and there is such an intense craving that the desire to drink remains the only interest in life. Sudden withdrawal of alcohol for any reason may lead to withdrawal syndrome. In addition, the alcohol-addict is liable to other neuropsychiatric syndromes such as Korsakoff's psychosis, hallucinosis, suicidal tendencies and Wernicke's encephalopathy. Apart from history and the obvious physical and mental degeneration, alcohol addiction can be diagnosed by demonstration of the drug in breath, blood or urine. Generally, there are associated changes due to nutritional deficiencies such as polyneuritis due to thiamine deficiency; anemia and edema. Chronic alcoholics may also suffer from hyperlipidemia, hyperuricemia, pancreatitis and hypomagnesemia.

The treatment of chronic alcoholism consists of:

(a) **Psychotherapy** : Alcohol addiction is often reversible if treated during early stages, if the addict realizes that his drinking has become a problem to him. An addict is a sick person sometimes with a feeling of guilt. One way to overcome this guilt is to convince the addict that he is an ill person. Outright condemnation of his taking a drink would do more harm. Psychotherapy by a sympathetic doctor can often give rewarding results. Complete co-operation by the patient is very necessary and he should be explained that indulgence in even small quantities of alcohol again would lead to a relapse. Psychotherapy forms the mainstay of treatment, supported by drugs which are used to establish a conditioned reflex so that the addict becomes averse to alcohol.

(b) **Drug therapy** : Drugs used for aversion therapy are Disulfiram (Antabuse) and Citrated calcium cyanamide (Carbimide).

DISULFIRAM (Tetraethyl thiuram disulphide) : Small doses do not have any action. The drug is administered as a 500 mg. tablet, once daily, for a week. Thereafter, the effect can be

maintained by administering 250 mg. daily. After a week's therapy, if a small amount of alcohol is given to the patient it produces toxic reactions, such as flushing, perspiration, palpitation, marked nausea, vomiting, fall of blood pressure and even collapse. The patient thus realises that while on this drug he cannot tolerate even small doses of alcohol and would abstain from drinking. Severe reactions can occur even with the test dose and hence, this treatment should be carried out in a hospital. Many cases in which disulfiram has produced violent reactions following alcohol ingestion resulting in death have been reported.

Mode of action : The drug interferes with the oxidation of acetaldehyde formed during the metabolism of alcohol. This raises the blood level of acetaldehyde which acts directly on the cardiovascular system. In addition, disulfiram also inhibits dopamine beta oxidase and thus interferes with the synthesis of noradrenaline. This causes depletion of catecholamines.

The drug is slowly and incompletely absorbed from the gut and is metabolised slowly.

Adverse reactions : The drug can cause drowsiness, nausea, headache, cramps, fatigability and a metallic taste in the mouth. Confusional state is rare. Severe acetaldehyde reaction is described earlier.

Contraindications to disulfiram:

- (1) Hepatic and circulatory diseases.
- (2) Uncontrolled diabetes mellitus.
- (3) In alcoholics with obvious personality changes. General anaesthetics or paraldehyde, which produce similar effects as alcohol, should not be administered simultaneously with this drug. Occasionally, this can cause severe reactions such as marked fall in blood pressure and collapse.

Other commonly used therapeutic agents producing similar but mild alcohol intolerance in some individuals are chlorpropamide, nitrofurantoin, griseofulvin, tolbutamide and phenylbutazone. Hence, the patient should be warned about such a possibility.

Carbimide, a drug with similar properties, has a shorter duration of action.

(c) Institutional therapy: Psychotherapy and drug therapy can be supported by institutional therapy where the patient can see for himself the ex-alcoholics who have become abstainers and are living a happy life. This can help to boost the patient's morale. A religious and spiritual approach is also useful.

In very chronic cases certain abnormalities of personality develop and the treatment becomes far more difficult. The results of aversion therapy with drugs are generally disappointing. Thus, in Korsakoff's psychosis there is a marked impairment of memory, disorientation in space, impaired physical capacity and diminution of will power.

Delirium tremens is rare (1%) but the most severe component of the abstinence syndrome which develops after sudden withdrawal of alcohol for some days in chronic alcoholics. The symptoms consist of restlessness, insomnia, tremors, hallucinations generally involving great fear, delirium and even convulsions. There is no specific treatment. Symptomatic treatment consists of :

- (i) Correction of dehydration,
- (ii) Use of sedatives such as benzodiazepines,
- (iii) Maintenance of nutrition; giving vitamins, particularly thiamine.

In case of alcohol addiction sudden and total withdrawal is usually effective because the withdrawal syndrome can be managed with other drugs like benzodiazepines and usually does not endanger life.

METHYL ALCOHOL : This is generally used in a 5% concentration to denature ethyl alcohol. Its absorption and distribution are similar as ethyl alcohol; the rate of metabolism, however, is very slow. It is mainly oxidized to formaldehyde and subsequently to formic acid, which is toxic. The latter reaction is folate dependent and causes folate depletion.

Pharmacological actions : Initially these

resemble those of ethyl alcohol and are due to CNS depression. Methyl alcohol poisoning usually results from ingestion of methylated spirit or adulterated wines. The symptomatology is due to CNS depression, acidosis following the production of formic and other organic acids (with marked elevation of the anionic gap) and the selective toxicity of certain metabolites like formaldehyde to the retinal cells. The symptoms may be delayed, particularly if ethanol is also consumed simultaneously. Usually, headache, vertigo, nausea, severe abdominal pain, dyspnoea and motor restlessness occur. Blood pressure is usually not affected but bradycardia has a bad prognostic significance. Coma can develop very rapidly, followed by death. In a very serious patient, the respiration is slow, shallow and gasping in type. Death is usually preceded by blindness. However, total blindness could occur with as little as 15 ml. of methyl alcohol while ingestion of 30 ml. is fatal.

Many deaths have been reported following the ingestion of methylated spirit for alcoholic effects.

Treatment of toxicity : This is directed towards correcting the acidosis as quickly as possible. The development of blindness, though not due to acidosis, is enhanced by acidosis. It must be emphasized that methyl alcohol is oxidised slowly and hence, acidosis can recur even after adequate initial alkali administration. It is necessary, therefore, to have close observation of the patient for several days to prevent sudden relapse and death. Treatment of metabolic acidosis is discussed in Chapter 33. Hypokalemia, if present, needs correction; so also the maintenance of adequate nutrition and water and electrolyte balance. The patient's eyes should be protected from strong light. Folic acid (1mg/kg upto 50mg) is administered I.V. every 4 hours for 6-7 days.

The infusion of ethyl alcohol has been recommended on the basis that it slows down the oxidation of methyl alcohol by competing for the same metabolic pathway. Ethanol administration can be life saving if, for some reasons, alkali therapy

is delayed.

ETHYLENE GLYCOL: This glycol (EG) is used as an antifreeze for automobile radiators and such products are the usual cause of EG poisoning. Ingestion of about 100 ml of EG, if untreated, can be fatal. EG is initially metabolized by hepatic alcohol dehydrogenase to glyoxal and glyoxylic acid. Further decarboxylation of glyoxylic acid gives rise to CO_2 and formic acid. Glyoxylic acid is also oxidized to oxalate. The glycol causes CNS depression and narcosis; oxalate and other intermediates are nephrotoxic and cause acute renal failure; formic acid produces severe metabolic acidosis with anion gap as high as 50 mEq/litre, as in the case of methyl alcohol.

Treatment of EG poisoning is similar to that of

methanol poisoning: ethanol and treatment of acidosis. Because of the associated renal failure, diuretics, urinary alkalization and early hemodialysis (which removes EG from the blood) are also indicated.

4-Methyl pyrazole is an inhibitor of alcohol dehydrogenase and has been found useful in the treatment of poisoning with methyl alcohol and EG. It is administered in the dose of 100 mg diluted in 250 ml of isotonic saline and infused slowly over 45 minutes. The inhibitory effect of the drug is rapid and prolonged. It is well tolerated and causes hardly any toxicity. Methyl alcohol and EG are rapidly cleared by the kidneys if the renal function is normal. Its use appears to be more effective than the use of ethyl alcohol.

5 General Anaesthetics

Priestley discovered the first inhalation anaesthetic, nitrous oxide, in 1776 and accurately described the sensations following its inhalation. It was used for the first time in 1844 by Horace Wells, a dentist in Hartford, U.K., for painless extraction of a tooth. Morton, in 1846 successfully showed the use of ether as a general anaesthetic in the first classic demonstration held in the operating room of the Massachusetts General Hospital, Boston, U.S.A. Since then the science of anaesthesiology has progressed considerably and many better agents are now available for use although an entirely satisfactory general anaesthetic agent is still not available.

The term anaesthesia means loss of sensation. General anaesthetics are the agents which bring about loss of all modalities of sensation, particularly pain, along with a reversible loss of consciousness. Local anaesthetics abolish the pain sensation in localized areas without affecting the degree of consciousness.

The general anaesthetic agents can be classified as :

I. Inhalation general anaesthetics:

(a) *Volatile liquids* : Chloroform; Diethyl ether; Ethyl chloride; Trichloroethylene; Halothane; Enflurane.

(b) *Gases* : Cyclopropane; Nitrous oxide.

II. Nonvolatile general anaesthetics (Intravenous anaesthetics).

(a) *Ultra short acting barbiturates* :

Thiopental sodium; Methohexital.

(b) *Non-barbiturates* :

(i) Eugenol derivative; Propanidid

(ii) Phencyclidine derivative; Ketamine

(iii) Steroid : Althesin

(iv) Etomidate

Site and mechanism of action of general anaesthetics : Although the general anaesthetic agents are capable of depressing all the functional elements of the central nervous system, it has been postulated that anaesthetics inhibit the ascending reticular activating system, which normally maintains a state of wakefulness. It is difficult to formulate a single theory about the mechanism of action of the general anaesthetics, as the individual agents differ widely in their physical and chemical properties. Enormous data about the modification of the various aspects of the central nervous system metabolism by the general anaesthetics is now available but the basic cause of these modifications remains obscure.

The fact that anesthesia can be achieved within a few minutes by compounds of varied nature and is rapidly reversible rules out any long term biochemical changes as basis for narcosis. The structural diversity of the various compounds suggests that anesthetics do not act at single specific receptor. However, as pointed out by Overton and Meyer, there is a close correlation between the potency of compound and its lipid solubility. Such correlation suggests that anesthesia results when a specific number of anesthetic molecules occupy a crucial hydrophobic site in the central nervous system. Since there is a relative resistance of larger axons to anesthetic induced depression, the hydrophobic site of action is probably localized to synaptic regions or axons with a small diameter at the nerve terminal. Anaesthetics, therefore, probably act by blocking excitatory synaptic transmission, but a few agents may act by prolonging synaptic inhibition. Both

presynaptic and postsynaptic actions are likely. How the interaction of anesthetic molecule with hydrophobic site produces anesthesia is not known, though various theories have been proposed. Although most investigators believe membrane lipids as the site of anesthetic action, others have postulated that general anesthetics directly inactivate proteins essential for central nervous system function. These agents may also release endogenous opiate like substances which are known to produce analgesia.

INHALATION GENERAL ANAESTHETICS

The administration of inhalation general anaesthetics demands an understanding of the fundamental laws of gases which govern their behaviour in the body. These are :

(a) *Boyle's law* : The volume of a gas varies inversely as its pressure, provided the temperature remains constant. Thus doubling the pressure halves the volume of the gas.

(b) *Dalton's law of partial pressure* : The pressure of a mixture of gases is the sum of the individual pressures of each gas; therefore, greater the concentration of the anaesthetic agent in the inhaled air, greater will be its partial pressure.

(c) *Henry's law of solubility* : According to this law, at a constant temperature the solubility of a gas in a liquid is proportional to its pressure. Hence, greater the partial pressure of the anaesthetic in the mixture the greater will be its solubility in blood.

(d) *Graham's law of diffusion* : The rates of diffusion of different gases are inversely proportional to the square root of their densities. The lower the density of an anaesthetic gas, the higher will be its rate of diffusion. The lighter gases, therefore, diffuse more rapidly into and out of the tissues.

(e) *Fick's law of diffusion of gases* : The rate of flow of a gas in one dimension is proportional to the diffusion coefficient and to the partial pressure and is inversely proportional to the linear

distance. The diffusion coefficient ($\text{cm}^2/\text{sec.}$) is inversely proportional to the square root of the density of the gas (Graham's law). In essence, the diffusion of the gas takes place from an area with a higher partial pressure to an area with a lower partial pressure.

The factors which control the transfer of the anaesthetic agents from the alveoli to the blood and from the blood to the tissues are :

(a) The solubility of the agent in the blood.

(b) The rate of blood flow through the lungs and the tissues.

(c) The partial pressure of the agent in the arterial and mixed venous blood and in the tissues.

The solubility of the anaesthetic agents varies considerably. Thus, diethyl ether is extremely soluble in blood, next comes halothane while agents like cyclopropane, nitrous oxide and ethylene are much less soluble. The more soluble an anaesthetic in blood, the more of it must be dissolved in blood to raise the partial pressure appreciably. As the partial pressure of the gas largely controls its rate of diffusion across the alveoli into the blood and from the blood into the tissues, the soluble anaesthetic agent may take a longer time to induce anaesthesia; this delay may be further increased by respiratory disturbances. Thus, it is difficult to induce anaesthesia with diethyl ether in the bronchitic-emphysematous patient. In such circumstances, it is advisable to induce anaesthesia with some other agent.

Compared to the conventional drugs, the general anaesthetics have a low margin of safety and the therapeutic indices vary from 2 to 4. It is also difficult to estimate the dose accurately. The anaesthesiologists describe the measure of potency of inhalation anaesthetic agents in terms of Minimum Alveolar Concentration (MAC) of the anaesthetic, at one atmospheric pressure, that produces immobility in spite of noxious stimuli in 50% of the patients or animals exposed to it. MAC, thus, represents a single point on the dose response curve for the production of anaesthesia. Usually, 0.5 to 2 MAC are required for adequate anaesthesia.

Stages of Anaesthesia : Guedel, in 1920, referring mainly to the anaesthetic activity of ether, outlined the four stages of general anaesthesia and divided the third stage of surgical anaesthesia into four planes. These stages can be distinctly discerned with the majority of the volatile general anaesthetics. However, in modern anaesthetic practice, the stages are never discerned separately. Every effort is made to achieve a smooth induction, avoiding the stage of delirium with the help of I.V. inducing agents such as thiopentone (see later). The stages are :

(I) Stage of analgesia. (II) Stage of delirium. (III) Stage of surgical anaesthesia. (IV) Stage of respiratory paralysis.

(I) Stage of Analgesia : This stage stretches from the beginning of inhalation of anaesthetic to loss of consciousness. The gradual depression of the cortical centres which develops during this phase is manifested as a sensation of remoteness, falling, suffocation or as visual or auditory aberrations. A feeling of warmth is experienced by some individuals. Even though minor surgical procedures such as incision of an abscess, dental extraction and obstetrical manoeuvres have been carried out successfully during this stage, the routine use of this stage for such procedures cannot be recommended as it is difficult to maintain it for a long time. With continued administration of the anaesthetic agent the patient passes into the second stage, the stage of delirium. Analgesia is produced before consciousness is lost.

(II) Stage of Delirium or Excitement : This stage extends from the loss of consciousness to the beginning of surgical anaesthesia. It may be associated with excitement, shouting, increased muscular activity, breath holding, tachypnoea and hyperventilation. Some of these manifestations are due to release of the lower centres from the inhibitory control of higher centres as a result of cortical depression. The pupils may dilate and marked hypertension and tachycardia may develop, probably due to release of adrenaline. Struggling, increased tone of the skeletal muscles,

retching and vomiting are the undesirable features of this stage and necessitate careful vigilance. However, these can be minimised by proper pre-anaesthetic medication.

(III) Stage of Surgical Anaesthesia : As more drug gets in, deep breathing starts and patient passes into the third stage. It is characterized by a gradual loss of reflexes, regular respiration and relaxation of the skeletal muscles. Reflex activity is lost. This stage is usually employed for surgical intervention and is divided into four planes. (Fig. 5.1).

Plane i : The pupils are normal in size and the eyeballs are roving. If the pupils are dilated before commencing the anaesthesia or reflexly during the second stage, they assume the normal size and then *dilate progressively with the depth of anaesthesia*. The respiration is full, regular, deep and of thoracoabdominal character. The blood pressure and the pulse rate are normal. The skeletal muscles are incompletely relaxed. The lid reflex, swallowing, retching and vomiting get abolished. The corneal reflex is present but the conjunctival reflex is lost. The loss of pharyngeal reflex in the middle of this plane enables the anaesthesiologist to pass a pharyngeal airway.

Plane ii : In the second plane, the eyeballs are fixed. The respiratory excursions are still regular but the amplitude is diminished. Muscular relaxation is adequate and the increase in respiratory rate or breath holding in response to skin incision is abolished. Reflexes arising from the larynx are also abolished and endotracheal intubation can be performed.

Plane iii : This is characterised by the beginning of asynchrony between the thoracic and the abdominal respiratory movements. The blood pressure begins to fall, the intercostal muscles are gradually paralysed and the respiration assumes an increasingly abdominal character. Thus, the costal margins retract with the descent of diaphragm in the later part of the third plane. The pupillary light reflex and the corneal reflex are lost. The muscular relaxation is essentially complete.

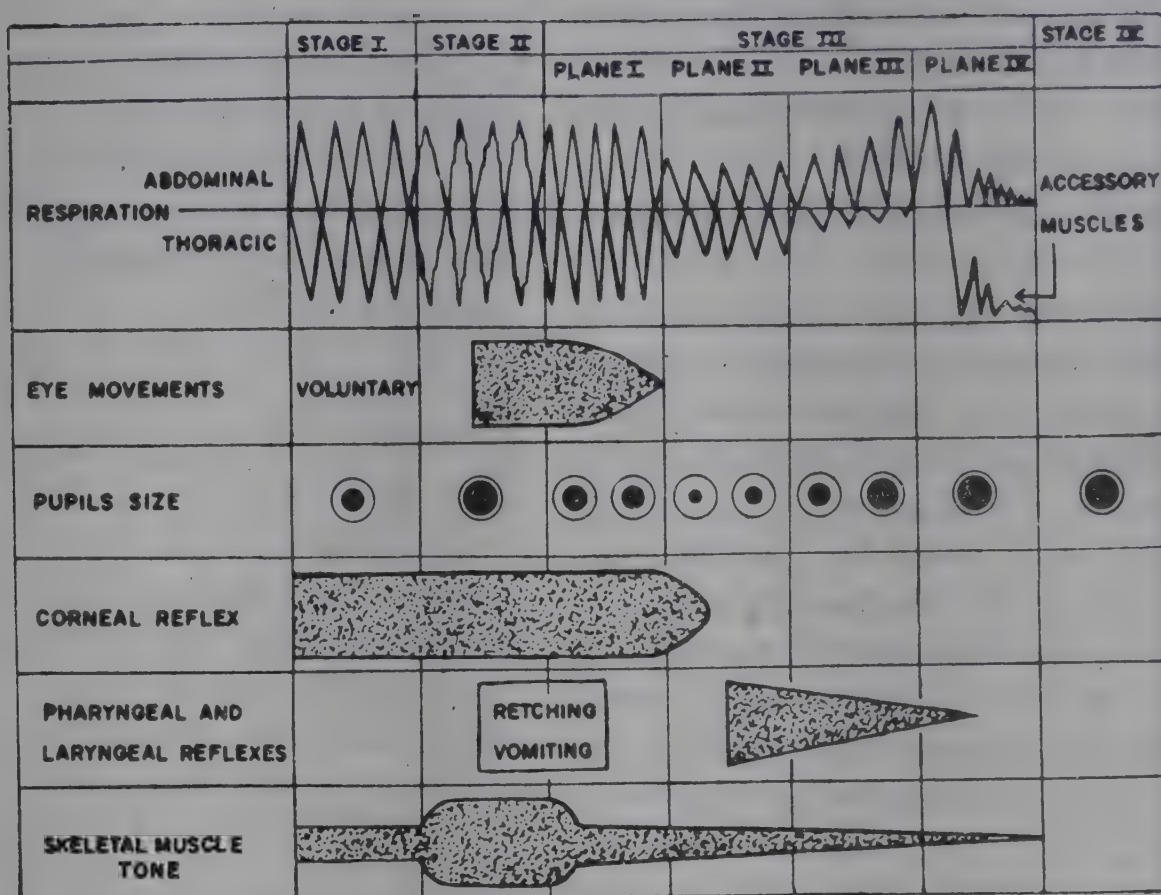


Fig. 5.1 : The Signs and Stages of Anaesthesia

Plane iv : The paralysis of the intercostal muscles is complete, the pupils are dilated, do not respond to light, the muscles are flaccid and the blood pressure is low. The secretions are progressively reduced from plane i onwards and are completely abolished in plane iv.

(IV) Stage of Respiratory Paralysis: This stage is characterised by severe depression of the vital medullary centres. Initially, as the diaphragmatic contractions become irregular, the accessory muscles of respiration may be brought into use but eventually complete respiratory arrest with the paralysis of accessory muscles and diaphragm supervenes. The respiratory arrest is also accompanied by vasomotor collapse and the heart ceases to beat.

The stages described here may differ considerably with different anaesthetic agents. Thus, cyclopropane induces apnoea in a far lighter plane of anaesthesia and halothane produces hypoten-

sion much more readily than ether. Pupillary dilatation is a progressive and reliable sign with ether and cyclopropane while it is insignificant with halothane. With ether the skin becomes pale, cold and wet in paralytic stage while with halothane, it is warm and dry until the development of marked hypotension. Preanaesthetic medication with the opioid analgesics, atropine and the use of skeletal muscle relaxants also modifies the signs of anaesthesia and may interfere with the proper assessment of the depth of anaesthesia.

In practice signs of autonomic nervous system activity (tachycardia, rise of blood pressure in response to stimulation, sweating and lacrimation), grimacing and other muscle activity all indicate inadequate anaesthesia. Loss of eyelash (lid) reflex and the development of rhythmic respiration indicate the beginning of surgical anaesthesia. Hypotension can be used as an index of

dosage with agents like halothane. Severe depression of respiration and marked hypotension or asystole indicate deep anaesthesia. The situation could be aggravated by associated blood loss and hypoxia. This must be avoided.

Methods of administration of general anaesthetics:

(a) *Open method*: This is a simple method of administering a volatile anaesthetic. A simple mask like Schimmelbusch mask covered with six to ten layers of gauze, which does not fit the contour of the face is held on the face and an anaesthetic like ether, chloroform or ethyl chloride is poured in drops. The anaesthetic vapour, diluted with air, is inhaled through gap between the mask and the face. The method does not need any anaesthesia apparatus. There is no re-breathing. This is also called an 'open drop' procedure.

(b) *Semi-open method*: This method is similar to open method but the dilution with air is prevented by using either a well fitting mask like Ogston's mask or layers of gauze between face and the mask. A small carbon dioxide build-up occurs with this method.

(c) *Semi-closed method*: This method allows some rebreathing of the anaesthetic drug with the help of a reservoir but in addition, part of the volume of each succeeding inspiration is a new portion from an anaesthetic mixture. This method involves accumulation and rebreathing of carbon dioxide.

(d) *Closed method*: This method essentially employs a chemical agent (soda lime) to reabsorb the carbon dioxide present in the expired air. It requires the use of a complicated apparatus but is particularly useful when the anaesthetic agent is potentially explosive.

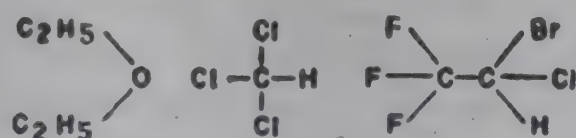


Fig 5.2: Ether

Chloroform

Halothane

VOLATILE LIQUIDS

The volatile general anaesthetics which are liquid at room temperature are all extremely potent but relatively soluble in blood, cell water and fat; hence, both induction and recovery with these agents are slower than that with the gaseous general anaesthetics.

DIETHYL ETHER: Anaesthetic ether contains 96-98 per cent diethyl ether. Ether is a colourless, volatile liquid with a pungent odour and with the boiling point 35°C. Ether vapour is irritating. Ether, when exposed to air, moisture or light may form ether peroxides or acetic aldehyde, which are irritant. To avoid this conversion, ether is marketed in sealed containers or amber coloured bottles covered with black paper. The containers are sometimes coated with copper as it retards the oxidation of ether. Ether is inflammable and mixtures of ether with air, nitrous oxide or oxygen may explode over the entire range of anaesthetically useful concentrations.

A concentration of 10-15 per cent of ether in the inspired air is usually required for induction while a concentration of 4 to 5 per cent ensures a satisfactory maintenance of anaesthesia in plane iii; with a concentration of more than 7 per cent respiratory failure may develop. Ether has a wide margin of safety.

Absorption, fate and excretion: Only a minor portion of ether is oxidized within the body; 85 to 90 per cent is eliminated through lungs and the remainder through the skin, urine, milk and sweat. Ether crosses the placental barrier and reaches comparable concentrations in the foetal blood.

Advantages of ether:

(a) It can induce surgical anaesthesia without any pre-anaesthetic medication. Ether is probably the safest anaesthetic, even in the hands of an inexperienced anaesthetist. It is an excellent analgesic and minor surgical operations can be performed even with subanaesthetic concentrations.

(b) Ether has a curarimimetic effect on skeletal muscles and produces satisfactory muscular relaxation. As it synergises with the muscle relax-

ant d-tubocurarine, the dose of the latter required to produce good muscle relaxation is less.

(c) Although ether depresses the response of the respiratory centre to carbon dioxide, the rate and volume of respiration are usually increased during ether inhalation. This has been explained as a reflex stimulant effect of ether on respiration, probably by stimulation of the sensory receptors in the tracheobronchial tree. Thus, during the ether anaesthesia, spontaneous respiration may be adequate even during planes i and ii of stage III anaesthesia. Although irritant to the upper airway, ether is a bronchodilator.

(d) Ether does not modify blood pressure during planes i and ii and does not sensitize the myocardium to adrenaline. Hence, it does not precipitate cardiac arrhythmias.

(e) Light ether anaesthesia does not interfere with the uterine contractility significantly and intermittent ether inhalation may be employed during delivery to reduce labour pains.

(f) Ether is devoid of significant hepatotoxicity and nephrotoxicity although temporary alterations in the liver function tests and a decrease in the urine flow may be noted. The latter is attributed to release of antidiuretic hormone and renal vasoconstriction.

(g) Ether can be administered without a complicated apparatus.

(h) Ether allows the use of air as a diluent and as a source of oxygen because the concentration required for anaesthesia is low. It is also economical.

Disadvantages:

(a) Induction is slow and is sometimes stormy, associated with marked excitement and thrashing.

(b) Irritant nature of the ether vapour may increase the salivary and bronchial secretions and induce cough and laryngeal spasm during induction.

(c) Because of its explosive nature cautery cannot be used along with ether anaesthesia. Even after cessation of ether anaesthesia it is safer not to

employ cautery for 10 to 15 minutes, as the ether in the exhaled air and that present in the body cavities is inflammable. Further, electrical sockets and switches situated within 1 meter of the floor should be spark-proof.

(d) During induction, sensitization of the baroreceptors by ether may produce reflex inhibition of the heart. However, the heart rate usually increases during ether anaesthesia as a result of increased sympathetic tone.

(e) Nausea and vomiting appear especially during recovery from ether anaesthesia but may also occur during induction.

(f) The recovery is slow. Alcoholics are tolerant to ether and induction of anaesthesia with ether in alcoholics may be difficult.

(g) Ether convulsions are uncommon but may occur in children. They are preceded by dyspnoea and cyanosis. In febrile children risk of potentially fatal ether convulsion is high. The cause is obscure. Ultrashort acting barbiturates are used to treat this emergency.

Ether rubbed into the skin produces local vasodilatation with a sense of warmth and pain (rube-facient action). It dissolves the sebaceous secretion and, in the form of ethereal soap, is used as a cleansing agent. It is used as a solvent.

CHLOROFORM, a powerful volatile liquid anaesthetic, used previously, is no longer recommended as a general anaesthetic. This is because of its toxicity, particularly the liver and cardiac toxicity, and smaller safety than that of other established drugs like halothane. For details, the earlier editions of this book may be consulted.

HALOTHANE (Fluothane). It is a fluorinated volatile anaesthetic with structural similarity to chloroform.

Halothane is a heavy, colourless liquid with a characteristic sweet odour and is supplied for anaesthesia in amber-coloured bottles. It has a fruity odour and boils at 50°C. It is stable in the presence of alkalis. Halothane readily attacks most of the metals including stainless steel, brass

and copper and may also affect the rubber elements of the anaesthetic equipment.

Halothane produces loss of consciousness in a concentration of 2 to 3 per cent in oxygen vapour and the anaesthesia can be maintained by using 1 to 2 per cent of halothane vapour with oxygen and nitrous oxide. A special apparatus is usually necessary to achieve a precise control of concentration.

Absorption, fate and excretion : About 60-80% of halothane is eliminated unchanged through lungs in the first 24 hours. About 15% appears to be retained in the body and is probably metabolised.

Advantages of Halothane :

(a) Halothane is non-inflammable and does not irritate the respiratory passage. It has a fruity odour and is not unpleasant for induction.

(b) Like chloroform, halothane is a potent anaesthetic. Induction of anaesthesia and recovery are reasonably quick. The incidence of post-operative vomiting is low.

(c) Halothane inhibits laryngeal and pharyngeal reflexes in upper planes of surgical anaesthesia to a considerable extent. It also relaxes the masseter muscles and inhibits salivation; hence tracheal intubation is much easier with this agent. It does not cause laryngospasm, bronchospasm, coughing, but produces bronchodilatation by a direct relaxation of the bronchial smooth muscle. Hence, it is preferred in patients with history of bronchial asthma.

(d) Halothane may be employed to induce controlled hypotension to provide a "bloodless" field during plastic surgery but is safe for this procedure only in expert hands.

Disadvantages :

(a) Muscular relaxation with halothane alone is inadequate to permit intra-abdominal operations; however, it potentiates the actions of d-tubocurarine, including its ganglion blocking effect and this may lead to profound hypotension during anaesthesia.

(b) Halothane depresses respiration if its concentration in the anaesthetic vapour is allowed to

exceed 2 per cent.

(c) It causes cardiovascular depression and hence, hypotension is a major drawback with halothane anaesthesia. It exerts a direct depressant action on the heart, decreases the cardiac output, reduces the sympathetic outflow and increases the parasympathetic tone. The total peripheral resistance changes very little even when hypotension occurs. With increased concentration it causes bradycardia. The normal baroreceptor mediated tachycardia in response to hypotension is reduced. With rapid inhalation or a sudden increase in the concentration of halothane, the blood pressure may decrease suddenly and cardiac arrest may supervene. A strict watch on blood pressure and pulse rate must be maintained during its use.

Halothane sensitizes the ventricular muscle and conduction tissue to adrenaline. It may increase the automaticity of the myocardium and may cause arrhythmias; usually, these are benign.

(d) Recovery of mental function after halothane takes several hours. Shivering during recovery is common.

(e) Hepatic damage including extensive hepatocellular necrosis, due to allergy or idiosyncrasy, following the use of halothane has been reported to occur after a period of 5 to 20 days after anaesthesia; its incidence is, however, very low. Individuals with hepatic disease and pregnant women are more likely to develop severe hepatotoxicity. Halothane should not be repeated at intervals of less than 3 months to avoid liver toxicity and should be avoided during pregnancy.

(f) Halothane is a poor analgesic and must be supplemented with nitrous oxide or opiates to provide satisfactory conditions for operation.

(g) Halothane is expensive and its use necessitates a special apparatus.

(h) Halothane causes rise in intracranial pressure due to cerebral vasodilation. Hence, it is contraindicated in patients with intracranial lesions.

ENFLURANE (Ethrane) : This halogenated volatile liquid anaesthetic is chemically 2-chloro-

1, 1, 2-trifluoroethyl difluoromethyl ether. It is non-inflammable with mild, sweet odour and boils at 57°C. It is very stable chemically. Anaesthesia produced by enflurane resembles closely that produced by halothane, except that the muscular relaxation is better and tachypnoea is uncommon. Like halothane, the compound causes hypotension and it potentiates the activity of non-depolarizing muscle relaxants. Further, it depresses myocardial contraction force and sensitizes the heart to the actions of catecholamines. There is no bradycardia and there is less tendency to tachycardia and cardiac arrhythmias. Like halothane, it causes bronchodilatation. The compound could produce seizures and involuntary motor activity during deep anaesthesia. Hence, it is relatively contraindicated in patients with epilepsy and brain lesions. About 80% of enflurane is excreted unchanged by lungs and only 2-5% is metabolised by liver. Liver damage is rare and in this respect enflurane appears to be superior to halothane especially when repeated anaesthesia is required.

ETHYL CHLORIDE : Ethyl chloride is a non-irritating, highly volatile and inflammable liquid with a boiling point of 12°C. The vapour has a characteristic but not unpleasant odour. When sprayed on the skin, it rapidly evaporates and thus cools the skin. This produces transient paralysis of cutaneous sensory nerve endings and local anaesthesia. If ethyl chloride spray is used as a local anaesthetic the skin should be prepared with petrolatum to prevent sloughing. The spray may produce local oedema with decreased resistance to infection and delayed wound healing. As the local anaesthetic effect lasts from a few seconds to a minute, only very minor operations such as incision of an abscess can be carried out within this time.

When used as a general anaesthetic, ethyl chloride induces anaesthesia within 1 to 2 minutes and recovery occurs within 2 to 3 minutes after its discontinuation. This makes the maintenance of a steady depth of anaesthesia extremely difficult.

The margin of safety is narrow. In addition, muscular relaxation is inadequate at safe depths of anaesthesia and the drug can damage the liver, induce cardiac arrhythmias and cardiac arrest. Because of its quick induction property it was used for induction of general anaesthesia.

TRICHLOROETHYLENE: Trichloroethylene is a clear, colourless liquid with a characteristic odour. It boils at 80°C. It is non-irritant and non-inflammable. It is usually coloured blue to distinguish it from chloroform.

Trichloroethylene is a potent analgesic with a rapid onset of action. However, muscular relaxation with this agent is inadequate. It may produce tachypnoea and even apnoea and sensitizes the myocardium to endogenous as well as exogenous adrenaline. The agent breaks down in the presence of soda lime to highly toxic product dichloroethylene and hence cannot be used in closed circuit. At present, its use is restricted as a supplement to nitrous oxide - oxygen combination to obtain a greater degree of analgesia. It has been used as a self-medication analgesic during labour in the form of intermittent inhalation.

The drug may cause nausea, vomiting and headache. Tachypnoea and cardiac dysrhythmias are dose related. It is contraindicated in raised C.S.F. pressure.

ISOFLURANE : This is a new, noninflammable liquid related to enflurane with uptake and excretion more rapid than halothane. Its pharmacological properties are similar to halothane but has much less action on the heart and is less liable to cause sensitization of the heart to catecholamines. The drug is metabolised only to the extent of 2%, further, it can be used even in patients with raised intracranial tension. Post operative nausea, vomiting and excitation are uncommon.

GASEOUS ANAESTHETICS

CYCLOPROPANE : Cyclopropane is a colourless gas with sweet odour and taste, supplied

as a liquid under pressure. It is administered in a closed circuit.

Its use requires a complicated apparatus and a trained anaesthetist. Anaesthetic mixture of cyclopropane and oxygen is explosive and this is its greatest disadvantage. It is also expensive. It is no more used. For details see earlier editions.

NITROUS OXIDE : Nitrous oxide is a colourless, inorganic, non-irritating gas with a sweet taste. It is non-inflammable and is marketed in steel cylinders at a pressure of 650 to 800 lbs. per square inch. The oxygen in the nitrous oxide molecule is not available for tissue respiration as nitrous oxide does not undergo significant decomposition in the body.

Nitrous oxide, if administered along with air, produces a stage of excitement and delirium and also produces amnesia. Hence the name "laughing gas".

Nitrous oxide produces analgesia when inhaled in the concentration of 35 to 40 per cent with air. Loss of consciousness occurs with the concentration of 65 to 70 per cent and plane I of surgical anaesthesia can be reached with an 80 : 20 mixture of nitrous oxide and oxygen. A further increase in the concentration of the anaesthetic agent produces hypoxia.

Absorption, fate and excretion : Nitrous oxide is not altered within the body and is carried in the form of a physical solution in the blood. It is rapidly eliminated through lungs within 2 to 5 minutes after its withdrawal.

Advantages of nitrous oxide :

(a) It is non-inflammable and non-irritating. It provides rapid induction and recovery.

(b) Because of its analgesic action in subanaesthetic concentration, nitrous oxide is employed for tooth extraction, for obstetrical analgesia, and for painful procedures such as changing dressing of burns, cleaning and debridement of wounds and cauterisation. Nitrous oxide is commonly used with oxygen and ether to maintain anaesthesia. The technique is termed "Gas-Oxygen-Ether (G-O-E) technique".

(c) Nitrous oxide is probably the safest of the anaesthetic agents, having no remarkable deleterious effects on circulation, respiration, liver and kidney. Unpleasant sequelae like nausea and vomiting are uncommon.

Disadvantages :

(a) Nitrous oxide is not a potent anaesthetic by itself and has to be supplemented with either pre-anaesthetic medication or with other potent anaesthetic agents or muscle relaxants to achieve surgical anaesthesia and muscle relaxation.

(b) Excitement may be violent.

(c) Carbon dioxide accumulation and hypoxia may develop during prolonged nitrous oxide anaesthesia, especially when supplemented with skeletal muscle relaxants. This may precipitate cardiac irregularities during anaesthesia.

(d) A special form of apparatus is necessary to control its administration.

(e) Any closed gas-filled space tends to expand during administration of nitrous oxide. It is therefore, contraindicated in patients with collections of air in the pleural, pericardial or peritoneal cavities; intestinal obstruction; occlusion of the middle ear; chronic obstructive airway disease; or emphysema. It is also contraindicated in patients who have recently undergone pneumoencephalography.

Other uses : Because of its transient action and inability to combine with haemoglobin, nitrous oxide has been used to measure the cerebral and coronary blood flow by Fick's principle.

Since modern surgery makes increasing use of electronic devices, inflammable and/or explosive anaesthetics like cyclopropane, ethyl chloride and ether are now considered obsolete in many advanced countries. *Ether, however, is being used extensively in many developing countries and is considered as a safe anaesthetic despite its inflammable and explosive nature.*

NON-VOLATILE GENERAL ANAESTHETICS

Ultra short acting barbiturates :

The ultra short acting barbiturates admini-

stered intravenously to produce general anaesthesia are the thiobarbiturates (thiopental, thiamylal and thiobarbitone) and the methylated oxybarbiturates (hexobarbitone and methohexitone). The compound employed most commonly is thiopental. (See Chapter 6).

THIOPENTAL: The sodium salt of thiopental is readily soluble in water but the solution deteriorates on keeping.

The clinically used solution is intensely alkaline with a pH varying from 10.5 to 11. High alkalinity causes local irritation and thrombosis. Given I.V. it rapidly induces hypnosis and anaesthesia without analgesia.

Anaesthetic action : The induction is very quick and pleasant. The subject passes through the stages of hypnosis and deep sleep to anaesthesia. Consciousness is lost first, then the reflex activity and muscle tone and lastly, the vital medullary centres are depressed. Pupils react to light and remain contracted in light hypnosis. There may be nystagmus or divergent strabismus. The corneal reflex remains active until deep anaesthesia is achieved. Cerebral blood flow and cerebral metabolic rate are reduced and there is a marked reduction of intracranial tension.

A fairly reliable sign of an adequate induction by thiopental is the absence of the eyelid reflex. Presence of swallowing, phonation and reflex movements of eyes during anaesthesia indicate further need for injection.

Though the reflexes return in 10-30 minutes, the patient remains disoriented for several hours and hence, must not be left alone.

Absorption, fate and excretion : The details are discussed elsewhere. The very short duration of action is attributed to its high lipid solubility. The plasma level diminishes as the concentration in fat increases. With successive doses body fat depots get saturated with the drug. Slow release of the stored drug back into the plasma is responsible for the continuation of drowsiness observed after the cessation of injection. The rapid metabolism of the drug by liver may also contribute to its short duration of action. It readily crosses the placental barrier and appears

in breast milk.

Uses :

- (1) Induction of general anaesthesia.
- (2) As anaesthetic agent for operations of short duration e.g. in fracture reduction, dilatation and curettage and dental procedures.
- (3) As anticonvulsant in the emergency treatment of convulsions.
- (4) A small I.V. dose is sometimes used to supplement local anaesthesia, mainly for quick sedative-hypnotic action.

Advantages of intravenous thiopental anaesthesia :

- (a) Ease of administration; nonexplosive.
- (b) Induction is rapid and pleasant with no irritation of the mucous membranes.
- (c) The incidence of vomiting and excitement is much less.
- (d) Quiet respiration, no sensitization of the myocardium to adrenaline.
- (e) Speedy recovery after small doses.
- (f) Low incidence of post-anaesthetic complications.

Disadvantages :

(a) The usual stages of anaesthesia are not discernible during intravenous barbiturate anaesthesia. During various stages the pupils are normal or constricted. The stage of surgical anaesthesia may be reached very quickly and constant supervision is necessary to prevent an overdose.

(b) During induction, unpleasant and even fatal reactions like apnea, coughing, hiccough, laryngospasm and bronchospasm may develop. Apnea should be treated with artificial respiration and oxygen administration. If sudden laryngeal spasm occurs, an attempt should be made to break through it. Use of succinylcholine and immediate intubation are advocated. *It is essential that the necessary equipment for controlled breathing is kept ready.*

(c) It depresses the respiratory centre, which becomes less sensitive to carbon dioxide.

(d) Barbiturates also depress the vasomotor centre and the myocardium. A rapid injection may produce hypotension and cardiac arrhythmia.

mias particularly in elderly, arteriosclerotic individuals and in those with reduced blood volume. Hence, it should be used carefully in patients with heart disease. *Further, it should never be given in sitting position in a dental chair as sudden deaths have been reported.*

(e) Muscular relaxation with thiopental is usually not adequate. The pharyngeal and the laryngeal reflexes are not abolished.

(f) Barbiturates are poor analgesics. Recovery from barbiturate anaesthesia is sometimes associated with restlessness and delirium. Shivering is frequent following prolonged barbiturate anaesthesia.

(g) It may cause silent regurgitation due to relaxation of the gastro-esophageal sphincter.

(h) Injection into or around a nerve (usually the median) may produce permanent palsy, while intra-arterial injection may give rise to intense vasospasm and sometimes the arm may have to be amputated because of gangrene.

Barbiturate anaesthesia is to be used with great caution in the presence of hepatic and/or renal damage, in shock, in airway obstruction, in individuals with a past history of bronchial asthma and severe cardiovascular disease. It is contraindicated in acute intermittent porphyria.

Preparations :

(i) Thiopentone sodium I.P. 0.5 to 1.0 g. powder. It is used as a freshly prepared, 2.5% solution for intravenous anaesthesia, as basal anaesthesia or for induction.

(ii) Methohexitone (Brevital) : Twice as potent as thiopental and claimed to be shorter acting. It is used as 1 per cent solution and is less irritant to veins but as damaging to the arteries as thiopental.

MIDAZOLAM is a short acting benzodiazepine which has been used either I.M. as a premedication; or I.V. for sedation for endoscopic procedures and for induction of anaesthesia. The I.V. dose is 2.5 to 7.5 mg; the usual I.M. dose is 5 mg. With I.V. administration of midazolam, the same

precautions are required as with I.V. diazepam. It is water soluble and less irritant to the veins than diazepam. (See Chapter 6).

PROPANIDID : Propanidid, a eugenol derivative, is an oily liquid. Given intravenously, it provides intense hypnosis and analgesia of short duration with recovery within 20 to 30 minutes. The compound, however, may produce involuntary movements such as twitching and tremors, a fall in blood pressure, laryngospasm, low grade haemolysis and respiratory depression. It is also reported to produce thrombophlebitis, nausea, vomiting, headache and excessive salivation. It produces hyperventilation and may cause anaphylactic reaction. It is now rarely used.

KETAMINE (Ketalar) : This non-barbiturate general anaesthetic agent is related to phencyclidine. It is effective by both intramuscular (5-10 mg/kg) and intravenous (1-2 mg/kg) routes. It has analgesic property in subnarcotic doses, and light anaesthesia usually does not cause depression of the protective pharyngeal and laryngeal reflexes. It probably acts on the cerebral cortex particularly the limbic system. Given intravenously, it is quick acting although the onset of action is slower than that of thiopental. Following a single dose, it induces a state of dissociative anaesthesia characterized by complete analgesia combined with amnesia. Analgesia lasts for about 40 minutes whereas anaesthesia lasts for about 15 minutes only. The pattern of sleep is different from that which occurs with barbiturates. The anaesthesia is sometimes associated with nystagmus, involuntary movements and hypertonus. The drug increases the blood pressure and can therefore, be used in the presence of shock. Muscular relaxation is poor. Intracranial and intraocular pressure rise and hence, it is not recommended for eye operations. During induction and recovery, it may cause delirium, hallucinations and unpleasant dreams, particularly in adults; this is an important disadvantage. Diazepam given intravenously rapidly abolishes these disturbances. Laryn-

gospasm may occur but rarely and salivation can be troublesome. The drug is presently advocated as an inducing agent and for maintenance of anaesthesia in children during short procedures like cardiac catheterization and bronchoscopy. It has been used in adults for such short procedures as the dressing of burns, forceps delivery, breech extraction, manual removal of the placenta and dental work.

Ketamine should not be used in hypertensives and in patients with cerebrovascular accidents or cardiac decompensation. It should be avoided for surgery of the pharynx, larynx and bronchi because it does not obtund reflexes arising in this area. It has a poor effect in relieving visceral pain and therefore, it is not recommended as an anaesthetic for abdominal surgery. A patient on thyroxine may develop a very marked rise in blood pressure following ketamine. Ketamine is contraindicated in pregnancy before term, since it has oxytocic activity. It is better suited for use during caesarean section, as it causes less fetal and neonatal depression.

Barbiturates and diazepam are chemically incompatible with ketamine. They should never be administered from the same syringe or via the same infusion set.

CT 1341 (Althesin) : This steroid anaesthetic is a combination of two pregnanedione derivatives, alphaxolone and alphadolone acetate. Given intravenously, it produces analgesia and sleep like hydroxydione. It is less irritant. Muscle twitching, involuntary movements, hiccough and allergic reaction may occur occasionally. Blood pressure and respiration, however, are not much affected. Its duration of action is between propanidid and methohexitone and unlike thiopental, the recovery is complete after a single dose. It has been used as an inducing agent in place of thiopental. It sometimes causes allergic reactions, including anaphylaxis probably due to the solvent used.

ETOMIDATE : This new intravenous anaesthetic agent has potent hypnotic and anaesthetic properties. A single I.V. dose of 0.3 mg/kg

produces loss of consciousness within 10 seconds and a state of anaesthesia, followed by sleep. Recovery is rapid and complete. Cardiovascular and respiratory changes are minimal. Rarely, it causes involuntary movements. It is contraindicated in patients with epilepsy.

NEUROLEPTANALGESIA

Neuroleptics (antipsychotics) are a group of drugs which induce a state of apathy and mental detachment in which the patient is mildly sedated and uncaring about his surroundings. These compounds are used in the treatment of major psychoses and are discussed in detail in Chapter 11. *Neuroleptanalgesia* is a method of intravenous anaesthesia which combines the use of a neuroleptic drug with a opioid analgesic drug which relieves pain. Administration of such a combination produces a state which differs from the classical general anaesthesia in that the subject is conscious and is able to co-operate during the operative procedure. Although various combinations have been used, the most favoured combination at present is that of a neuroleptic droperidol and an analgesic fentanyl (Innovar, Neurodol, Fentanyl).

DROPERIDOL : This is a butyrophenone derivative like haloperidol. Its pharmacological actions are similar to those of chlorpromazine (see Chapter 11). The drug is short acting (2-3 hours) and more potent than haloperidol. Apart from typical behavioural effect of calming, droperidol also has an antiemetic and alpha-adrenergic blocking (adrenolytic) action. Like all neuroleptic drugs it can produce extrapyramidal disturbances.

FENTANYL : This drug belongs to the group of 4-acylanilino piperidines. It is a morphine-like opioid analgesic (see Chapter 8) used exclusively as a supplementary analgesic in inducing general anaesthesia. Like morphine, it suppresses the respiratory and cough centres and causes nausea,

vomiting and miosis. It is 100 times more potent than morphine, milligram for milligram. However, its action is of shorter duration. Given intramuscularly or intravenously it rapidly produces profound analgesia, and other morphine-like effects lasting for about 30 minutes. Like morphine, these actions are antagonized by naloxone.

In clinical practice, the combination usually preferred contains droperidol 2.5-5 mg. and fentanyl citrate 0.05-0.1 mg. Given intravenously it causes complete analgesia, without marked hypnosis, sufficient for surgical procedures. The onset of anaesthesia is slow. Major advantages of this procedure are : (1) smooth onset and rapid post-operative recovery, (2) much less danger of hypotension and other circulatory disturbances, (3) suppression of vomiting and coughing, (4) continued analgesia in postoperative period and (5) availability of patient's co-operation during the operative procedures such as eye, oral and orthopaedic surgery, angiocardiology, myelography and bronchoscopy. Since the combination does not disturb the cardiovascular dynamics it is claimed to be very useful in old people and in 'poor risk' cases. Further, the combination can be used to induce anaesthesia which can then be continued with other general anaesthetic agents like nitrous oxide-oxygen mixture and muscle relaxants.

Possible adverse reactions are due to toxicity of individual drugs and are usually mild. They include hallucinations, mental depression, extrapyramidal disturbances due to droperidol and respiratory depression due to fentanyl. The latter may be marked and assisted, controlled ventilation is necessary. As compared to droperidol, fentanyl has a shorter duration of analgesic action (30 minutes) and supplementary doses of fentanyl (1 µg/kg) may be given after 20 minutes, if necessary.

PRE-ANAESTHETIC MEDICATION

Pre-anaesthetic medication is the term applied

to the use of drugs prior to the administration of an anaesthetic agent, with the important object of making anaesthesia safer and more agreeable to the patient. The reasons for such medication are:

(a) For sedation, to reduce anxiety and apprehension without producing much drowsiness.

(b) To obtain an additive or synergistic effect so that induction could be smooth and rapid and the dose of the general anaesthetic could be reduced.

(c) To relieve preoperative and post-operative pain.

(d) To suppress respiratory secretions and to reduce reflex excitability.

(e) To counteract certain adverse effects of the anaesthetic drug used such as salivation, bradycardia and vomiting.

There is no single drug which can achieve all these objectives and hence usually a combination of drugs is used. It must be emphasized, however, that factors other than drugs can favourably affect preoperative psychological preparation and a preoperative visit by the anaesthesiologist and a sympathetic discussion with the patient about the events of the next day in itself have a high therapeutic value.

The drugs commonly used for preanaesthetic medication are :

(1) Opioid analgesics e.g. morphine (10-15 mg. I.M.), pethidine (50-100 mg. I.M.), buprenorphine (0.3 mg. I.M.), are commonly employed for their sedative and analgesic properties. Buprenorphine has longer duration of action than morphine and pethidine. They also reduce the amount of general anaesthetic required. However, they have certain disadvantages :

(i) They may depress respiration and may produce respiratory arrest even before surgical anaesthesia is induced. Further, drugs like morphine increase the tone of smooth muscle such as bronchial muscles. In emphysema or in kyphoscoliosis where the pulmonary reserve is already low, use of opioids may precipitate pulmonary insufficiency.

(ii) By causing vasomotor depression, they decrease the ability of circulation to respond to stress. It often delays the awakening as its clinical effect lasts for 4-6 hours

(iii) Morphine may induce vomiting; besides it has an antidiuretic effect.

(iv) Morphine can interfere with pupillary reactions.

(v) Pethidine may produce tachycardia by its vagolytic action.

(vi) Both these drugs are histamine liberators.

(2) Barbiturates and tranquillizers : Drugs like pentobarbitone and secobarbitone are used to provide sedation and to relieve apprehension. These drugs, however, are not analgesics and hence the incidence of emergent excitement tends to be higher. Non-barbiturate sedatives like chloral hydrate and paraldehyde may also be used. However, tranquillizers like benzodiazepines (diazepam, nitrazepam) are now preferred to barbiturates because of their safety, muscle relaxant property and less respiratory depression. They also provide amnesia. Diazepam in doses of 5 to 20 mg. has been most widely used. It is active orally and can also be given parenterally, though its action is less predictable by this route. Other tranquillizer compounds used belong to phenothiazine and butyrophenone groups. They exhibit similar properties. Phenothiazines possess sedative, antiarrhythmic, antiemetic and antihistaminic properties. They, however, can potentiate the effects of barbiturates and morphine and may cause respiratory depression and arterial hypotension. Phenothiazines commonly employed are promethazine, 25 mg and trimeprazine (Vallegran). They can be given orally as well as parenterally (See Chapter 11).

(3) Anticholinergic drug such as atropine (0.6 mg. I.M.) or scopolamine is generally combined with morphine to block the vagal actions so as to reduce salivary and respiratory secretions and to prevent reflex parasympathetically induced hypotension and bradycardia. It may thus lessen the possibility of cardiac arrhythmias during the induction stage. Atropine stimulates the

C.N.S. while scopolamine has a central depressant action. Due to blockade of cardiac vagal action, these drugs may produce tachycardia. One must remember that atropine causes initial vagal stimulation by its central action; use of atropine in combination with neostigmine to reverse the neuromuscular blockade by the muscle relaxant d-tubocurarine, therefore, may sometimes cause cardiac arrest and death. Synthetic anticholinergics such as glycopyrrolate, a long acting quaternary amine, can be used instead of atropine for this purpose and are sometimes preferred because of their less central actions and less tendency to cause excessive tachycardia.

(4) Antiemetics : The commonly used phenothiazines such as promethazine and trimeprazine have antiemetic properties and thus may help to prevent the post-operative nausea and vomiting. This advantage should, however, be weighed against the possible hypotension following these drugs. Other drugs used are cyclizine, 50 mg., trimethobenzamide 200 mg and benzquinamide 25-50 mg.

(5) Other drugs : In addition to above mentioned drugs, proper pre-evaluation and specific premedication is needed in patients with special problems such as chronic lung disease, emphysema, coronary heart disease, diabetes mellitus, hypertension, undernutrition and in debilitated and old people.

DRUGS ADMINISTERED DURING ANAESTHESIA

These are :

(a) Skeletal muscle relaxants like succinylcholine and d-tubocurarine to achieve good muscle relaxation (See Chapter 18).

(b) A very short acting ganglion blocking agent like trimethaphan camphor sulfonate or sodium nitroprusside to produce controlled hypotension (See Chapter 26).

(c) Drugs administered to counter the anaesthetic complications e.g. vasopressor agents (such as methoxamine or phenylephrine) to cor-

rect hypotension, anti-arrhythmics to correct cardiac arrhythmias, anti-convulsants and respiratory stimulants.

The prophylactic administration of supplementary steroids to patients receiving steroid therapy or those with a history of such therapy within two years prior to surgery is necessary to avoid serious hypotension and shock during surgery. Antibiotics like streptomycin and neomycin have neuromuscular blocking action and hence, can produce skeletal muscle paralysis when instilled into pleural or peritoneal cavities during anaesthesia; these drugs can also potentiate the actions of skeletal muscle relaxants like d-tubocurarine. Patients on beta-adrenergic blockers tend to develop hypotension more often following certain anaesthetic agents.

REQUIREMENTS OF AN IDEAL ANAESTHETIC AGENT

For patient : It should be pleasant to inhale

without any irritation. The induction should be fast and pleasant and the recovery smooth and rapid. It should not produce any toxicity.

For surgeon : It should produce good analgesia and adequate muscular relaxation. Capillary bleeding should be negligible and it should not be explosive.

For anaesthetist : It should be stable at room temperature and be easily controllable with a wide margin of safety. It should not cause respiratory or circulatory depression and should be readily eliminated from the body.

It should not attack the material used for anaesthesia e.g. rubber tubing and metal.

A complicated apparatus should not be required for its administration.

For manufacturers : Cost of production should be cheap and should have no storage problems.

6 Sedatives, Hypnotics and Pharmacotherapy of Insomnia

Physiologically, sleep is still regarded as absence of wakefulness; brain stem mechanisms are actively involved in the process of falling asleep and its maintenance. However, electrical stimulation of many parts of the brain induces sleep, indicating an active phenomenon, related to definite anatomic structures as well as to specific biogenic amines. We all need sleep. The determinants of natural sleep are many but the most important regulator is the biological clock, the 24 hour daily rhythm. It is believed that growth and restoration of tissues take place chiefly during sleep, and the association between sleep and growth in the early years of life is generally accepted.

The electroencephalogram (EEG), the electro-

oculogram (EOG) and the electromyogram (EMG) can be conveniently recorded during sleep by fixing small silver electrodes to the scalp and to the face before the subject goes to bed. EOG reveals the eyeball movements while EMG indicates the tension of the muscles. Based on these records two kinds of sleep can be identified. In one the EEG contains 'sleep spindles' and prominent slow waves, the eyeballs remain motionless and the muscles under the chin remain tense. This is known as non-rapid eye movement (NREM) or slow wave sleep. In the other type, the EEG shows no spindles, the eyeballs make rapid jerky movements and the muscles are profoundly relaxed; this pattern is known as rapid eye movements

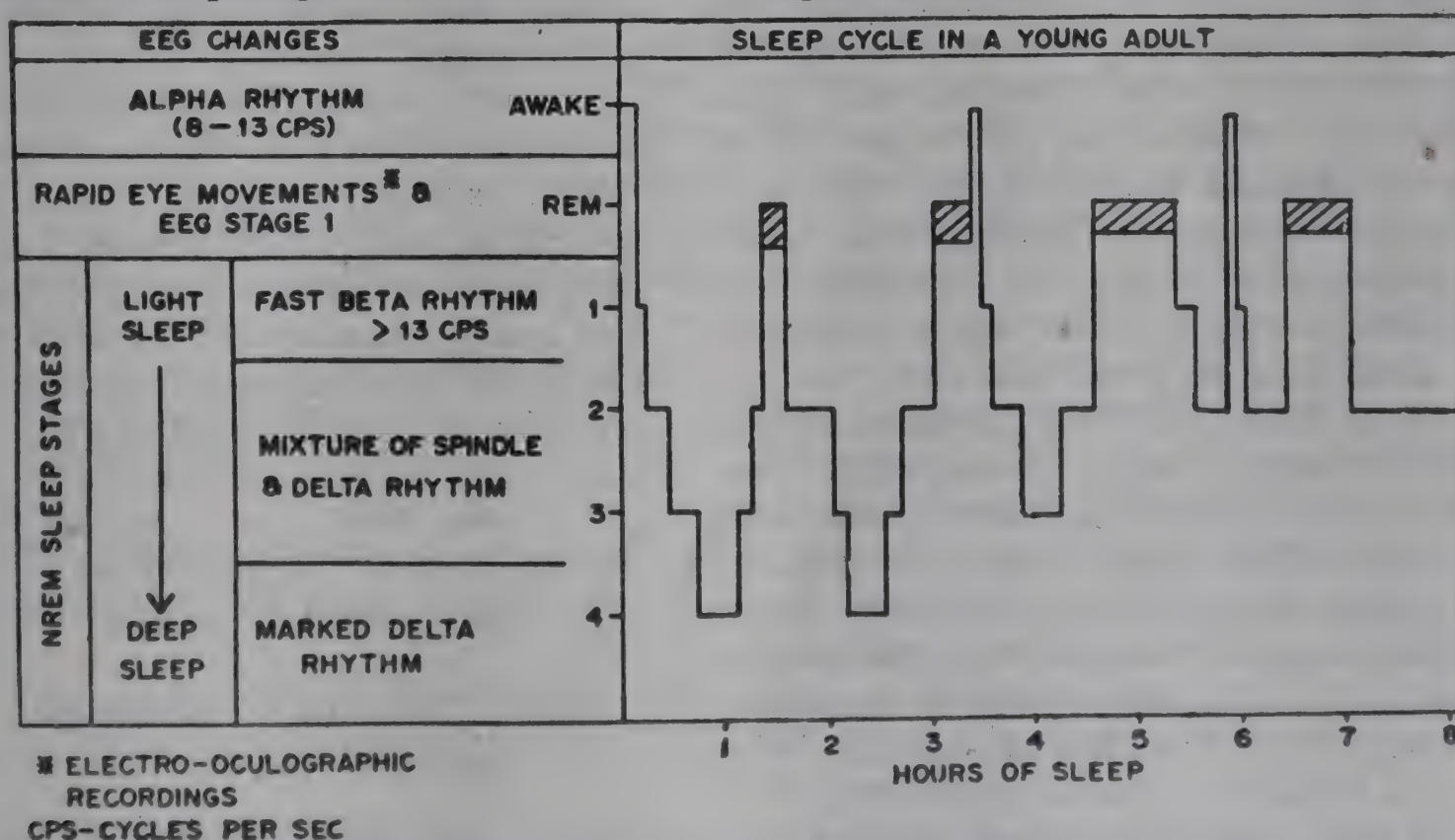


Fig. 6.1 : Sleep cycle and EEG changes in a normal young adult. Shaded area denote REM sleep.

(REM) or the paradoxical sleep. Tachycardia and rise of blood pressure are seen during REM sleep (Fig. 6.1).

The NREM sleep can be subdivided into stages 1, 2, 3, and 4, where stage 1 is a stage of drowsiness and stage 3 and 4 represent profound sleep. During NREM sleep, growth hormone secretion is at its greatest. Simple rest without sleep is not sufficient to release the growth hormone. The restorative properties of sleep may be attributed to such release of active substances during sleep.

The REM sleep is accompanied by dreaming; seventy-five percent dreams occur in REM sleep. Further, they are more vivid, sexual and bizarre than in non-REM sleep. In the male, REM sleep frequently begin with an erection. The profusion of rapid eye movements correlates with the vividness or activity of the reported dream events. During this stage, the activity of individual neurones has been shown to be increased, sometimes reaching the levels found during the waking stage and hence the name 'paradoxical'. Further, the cerebral blood flow exceeds even that during the waking state.

The popular notion that sleep is a uniformly quiescent and peaceful state and therefore, devoid of stress is not correct. In a normal young adult NREM sleep precedes REM sleep which occurs cyclically throughout the night at intervals of about 90 minutes. REM sleep occupies about 20-25% of total sleep time. These normal patterns are known to be altered by various diseases, sleep disorders and drugs, but the clinical significance of these alterations is still uncertain.

A normal person spends approximately one-third of his life in sleep. Adequate sleep is a necessity of life. A significant number of individuals complain of lack of sleep, insomnia, and the use of hypnotics and sedatives is, therefore, on the increase, often indiscriminately as evidenced by the availability of large number of such preparations in the market and the high incidence of addiction and acute poisoning due to hypnotic drugs.

A *hypnotic* drug is one which produces sleep resembling natural sleep. A *sedative*, on the other

hand, is a drug that reduces excitement. Hypnotics and sedatives both induce depression of the central nervous system, the difference being mainly quantitative.

Classification of hypnotics :

I. Urea derivatives :

(a) Diureides--barbiturates.

(b) Related ureides--glutethimide, methypylone.

II. Benzodiazepines.

III. Alcohols--chloral hydrate

IV. Aldehydes--paraldehyde.

V. Acetylated carbinols--ethinamate.

VI. Miscellaneous : Meprobamate, methaqualone, antihistaminics and scopolamine.

VII. Inorganic ions--bromide.

Drugs like morphine and pethidine, besides acting as analgesics, also possess hypnotic property. Hence, they are grouped as *Anodyne hypnotics*. It must be emphasized, however, that they should not be used as hypnotics in the absence of severe pain.

UREA DERIVATIVES

BARBITURATES, the derivatives of barbituric acid, were in the past the most commonly employed hypnotics.

The basic compound barbituric acid is a condensation product of urea with malonic acid and consists of a six membered ring structure. Barbituric acid itself is devoid of any hypnotic activity. The hypnotic activity is conferred by replacement of the hydrogen atoms attached to carbon atom at position 5 by aryl (containing a ring structure) or alkyl (straight chain) radicals (Fig. 6.2).

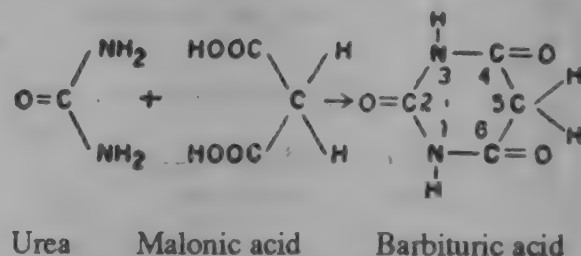


Fig. 6.2 : Synthesis of barbituric acid

The substituted forms of barbituric acid are colourless, odourless, crystalline solids with a

bitter taste and are only sparingly soluble in water. They dissolve rapidly in the organic solvents like chloroform and ether. The sodium salts of these compounds form alkaline solutions in water; such solutions are unstable during heating or even when kept at room temperature for a long time.

Structure activity relationship : The hypnotic potency and the duration of action of barbiturates is modified by changes in their chemical structure. An increase in the length of the side chain (aliphatic or aromatic) attached to the C5 carbon atom increases the lipid solubility, decreases the latent period of action and increases the rate of metabolic degradation, thereby shortening the duration of action of the compound e.g. hexobarbitone. However, when the chain length exceeds four or five carbon atoms, activity begins to decrease and convulsant properties may appear. When the sum of the carbon atoms in both chains exceeds eight, toxicity increases more rapidly than the therapeutic utility.

Introduction of a phenyl group in the side chain at C5 reduces the hypnotic properties but the compound acquires an anticonvulsant effect e.g. phenobarbitone.

Replacement of the oxygen attached to C2 by sulphur enhances markedly the lipid solubility of the compounds. Such compounds (*thiobarbiturates*) exist as yellow powders and because of rapid onset and short duration of action they are used for intravenous anaesthesia. The barbiturates which have an oxygen attached at C2 are called *oxybarbiturates* e.g. phenobarbitone and quinalbarbitone.

Conventionally, the barbiturates are divided according to their duration of action as :

(A) **Long acting** (8 hours or more) e.g. phenobarbitone.

(B) **Intermediate acting** (4 to 8 hours) e.g. amylobarbitone, butobarbitone, and pentobarbitone.

(C) **Short acting** (less than 4 hours) e.g. secobarbitone (quinalbarbitone) and hexobarbitone.

(D) **Ultra short acting (I.V.)** : thiopentone, kemithal, thialbarbitone and methohexitone

(see Chapter 5).

The elimination half lives, however, do not conform to the apparent duration of action. Further, the therapeutic doses of the various drugs are not necessarily equipotent as depressants of the central nervous system. Thus, phenobarbitone in therapeutic doses is a much less potent hypnotic than pentobarbitone.

Pharmacological actions : Barbiturates cause reversible depression of the activity of all excitable tissues, the CNS being exquisitely sensitive. However, hypnotic doses produce very little effects on cardiac, smooth or skeletal muscles. The exact mechanism of barbiturate depressant action is not known; they are believed to facilitate inhibitory neuro-transmission in the CNS, presumably by interacting with proteins of the gamma-amino-butyric acid (GABA) chloride ionophore complex to open chloride ion channels and hyperpolarize neuronal membrane.

Central Nervous System : Barbiturates can achieve various depths of depression of the central nervous system from a mild sedation through hypnosis to general anaesthesia. They depress the polysynaptic responses and delay synaptic recovery. Small doses may have G.A.B.A. like action.

(i) **Sedation and hypnosis :** The long and the intermediate acting barbiturates are used for this purpose. Thus phenobarbitone given in the dose of 15 mg. 3 to 4 times a day acts as a daytime sedative while pentobarbitone or quinalbarbitone in the dose of 100 to 200 mg. is used for induction, maintenance or prolongation of sleep. Given orally, the hypnotic effect appears within 15 to 30 minutes and is maintained for 4 to 5 hours. The sleep is claimed to resemble natural sleep. But, REM sleep is suppressed during barbiturate administration and a rebound increase in REM sleep occurs on withdrawal of barbiturates. This can lead to increased dreaming and even nightmares during the withdrawal period especially in addicts. Moreover, a hangover effect (residual sedation and headache on waking) is common after barbiturates.

Barbiturates used as sedatives reduce anxiety but may cause distortion of judgement. They also

impair vigilance and attention to external stimuli. Hypnotic doses of barbiturates produce motor incoordination.

If the ingestion of a hypnotic dose of a barbiturate does not induce sleep, the subject may experience euphoria. In old people and children, however, barbiturates may occasionally produce dysphoria or excitement and a state of confusion.

(ii) *Anaesthetic effect* : The short acting thiobarbiturates administered intravenously produce basal or general anaesthesia. These are discussed in Chapter 5.

(iii) *Anticonvulsant effect* : All the barbiturates administered in anaesthetic doses are capable of inhibiting or abolishing drug induced convulsions and those due to epilepsy and tetanus. However, phenobarbitone and mephobarbitone have a selective anticonvulsant action and are used for prevention of grand mal epileptic seizures (see Chapter 7).

(iv) *Analgesic effect* : Unlike the opioid and antipyretic analgesics, barbiturates do not lessen the pain sensation without producing a loss of consciousness.

(v) *Respiration* : Respiration is normally maintained as a result of

(1) a 'neurogenic drive' originating in the reticular activating system.

(2) a 'chemical drive' depending upon the concentration of carbon dioxide and pH of the arterial blood which directly modify the activity of the medullary respiratory centre and

(3) a 'hypoxic drive' mediated through the carotid and the aortic body chemoreceptors.

Sleep induced by hypnotic doses of barbiturates is associated with greater depression of the respiratory system than the normal sleep. Increase in the dose of barbiturates initially results in abolition of the 'neurogenic drive' followed by a decrease in the sensitivity of the medullary centres to carbon dioxide and changes in the pH. With toxic doses of barbiturates the respiration is maintained mainly by the 'hypoxic drive'. A further increase in the barbiturate concentration abolishes the hypoxic drive and also produces a direct paralysis of the medullary centre. Respira-

tory failure may be abetted by other factors like hypostatic pneumonia and pulmonary edema. Persons with pulmonary emphysema are very sensitive to the respiratory depressant action of barbiturates.

(vi) *Spinal cord* : Both the polysynaptic and the monosynaptic reflexes of the spinal cord are depressed by barbiturates.

(vii) *Eyes* : Hypnotic doses of barbiturates have no demonstrable effect on the eyes. A moderate increase in the dose, however, may elicit nystagmus. Nystagmus may also appear with therapeutic doses in patients with brain damage.

Barbiturates in small doses are claimed to depress initially the reticular inhibiting system. This initial depression can explain the increased sensitivity to pain and E.E.G. activation seen with small doses of barbiturates. Therapeutic doses bring about a depression of both the inhibiting as well as the activating systems; this results in hypnosis, with a characteristic sleep pattern (high voltage, low frequency) in E.E.G.

Cardiovascular system : Therapeutic doses of barbiturates may cause a slight fall in blood pressure and a decrease in heart rate as occurs during natural sleep. The decrease in blood pressure may be marked in hypertensive subjects.

Toxic doses of barbiturates produce a sustained hypotension as a result of (i) direct depression of the myocardium and the vasomotor centre, (ii) hypoxia and (iii) probably, blockade of sympathetic ganglia.

Gastrointestinal tract : Sedative doses of barbiturates do not affect the motility of the gut significantly. Toxic doses of barbiturates retard peristalsis.

Kidney : A hypnotic dose of a barbiturate does not significantly affect the urine output more than that observed during sleep. Intravenous barbiturate anaesthesia however results in reduction of urinary output as a result of decrease in the glomerular filtration rate, and stimulation of secretion of A.D.H. Acute barbiturate poisoning is often associated with oliguria largely due to severe

hypotension.

Liver : In the therapeutic dose range, barbiturates have no effect on normal hepatic function. However, in patients intolerant to barbiturates, hepatic involvement may occur along with dermatitis and damage to other parenchymatous organs.

Barbiturates exert remarkable actions on certain liver functions. Thus, they combine with cytochrome P-450 and thus competitively interfere with the biotransformation of a number of substrates of this enzyme.

Barbiturates, even those that do not undergo significant hepatic detoxification, stimulate the microsomal enzyme systems responsible for drug inactivation. This may explain the phenomenon of tolerance to barbiturates. Barbiturates also stimulate the hepatic metabolism of certain other agents, such as the oral anticoagulants, the antiepileptic drug diphenylhydantoin, vitamin K and D, doxycycline, steroid hormones, cholesterol, bile salts and the analgesic-antipyretic phenylbutazone, and this may reduce the clinical efficacy of these compounds if given along with or after barbiturates. This enzyme-inducing effect is not limited to the microsomal enzymes; other enzymes such as delta-amino-levulinic acid (ALA) synthetase, a mitochondrial enzyme, and aldehyde dehydrogenase, a cytoplasmic enzyme, are also induced. Increase in ALA synthetase results in an increase in ALA and porphobilinogen synthesis. In patients suffering from acute intermittent porphyria, the barbiturates may precipitate a severe attack resulting in paralysis and even death.

Phenobarbitone increases the hepatic glucuronyl transferase and the bilirubin-binding Y-protein.

Absorption, fate and excretion : Barbiturates and their salts are readily absorbed orally and intramuscularly. They are weak acids and the maximum absorption occurs from the stomach where the barbiturates exist in an unionized form. Satisfactory absorption also occurs from the intestine and the rectum. Given orally, sodium salts are uniformly and rapidly absorbed but because of

their extreme alkalinity, they may cause epigastric distress.

Following absorption, a fraction of the barbiturate in blood is reversibly bound to plasma albumin. The barbiturates are distributed in all tissues and body fluids. They readily cross the placental barrier and small amounts may be secreted in milk. No harmful effects on the suckling infant are known.

The factors which affect the distribution and fate of the barbiturates are their lipid solubility, degree of protein binding and the extent of ionization. The short acting barbiturates are highly soluble in lipids. As the biological membranes are mainly lipoidal in character, these compounds have a rapid onset of action and are more rapidly metabolized, but at the same time tend to get completely reabsorbed by the kidney tubules.

Barbiturates exist in the plasma in an ionized and a non-ionized form. The ionized form does not cross the biological membranes and cannot be reabsorbed by the kidney tubules. An increase in pH of blood and urine increases the ionization of the barbiturates causing an efflux of barbiturates from the tissues into the plasma. It also prevents their reabsorption by the kidney tubules and increases their excretion.

The activity of the barbiturates is mainly terminated by redistribution, metabolic degradation by the liver and renal excretion.

All barbiturates are metabolized, principally to inactive compounds, by the microsomal enzymes in the liver. The inactive metabolites are conjugated with glucuronic acid and are excreted in the urine. In the case of phenobarbitone, however, 25 - 30% of the dose is excreted unchanged. Hence, in the event of renal damage, it is safer to administer compounds like pentobarbitone which are completely metabolized by the liver, instead of phenobarbitone.

Preparations and dosage : The number of barbiturates available far exceeds their usefulness and only the important preparations are given in Table 6.1.

Therapeutic uses of barbiturates :

(a) As sedative-hypnotics: Although bar-

biturates can be used for this purpose, they have now been largely replaced by benzodiazepines because of certain advantages of the latter (see later).

(b) **As anticonvulsants** : The barbiturates have been used for controlling convulsions in eclampsia, status epilepticus and during spinal anaesthesia (See Chapter 7). However, they have now been largely replaced by benzodiazepines, particularly diazepam. The use of phenobarbitone in epilepsy is discussed in Chapter 7.

(c) **Preanaesthetic medication** : Barbiturates are sometimes employed as sedatives but benzodiazepines are now preferred for this purpose.

(d) **General anaesthesia** : See Chapter 5.

(e) **Psychiatric uses** : Amylobarbitone, pentobarbitone or thiopentone is employed by intravenous route to produce a state of deep sedation in which the cortical inhibitions are removed. This may bring forth the suppressed psychic disturbances; the patient becomes more communica-

tive and amenable to suggestions. This procedure of narcoanalysis is useful in certain psychiatric disorders like anxiety states and hysteria.

(f) **Miscellaneous uses** : Barbiturates are used to activate the latent E.E.G. abnormalities in certain cases of psychomotor epilepsy in children. Phenobarbitone stimulates the liver to produce glucuronyl transferase, the enzyme essential for metabolism and excretion of bilirubin. It is, therefore, used to treat certain types of neonatal jaundice.

Adverse reactions :

(a) **Intolerance** : Abnormal reactions may be manifested as excitement with hypnotic doses or appearance of headache, nausea, vomiting, diarrhoea and lassitude. Occasionally, barbiturates themselves may produce paroxysmal pain resembling neuralgia, myalgia or arthritis, particularly in the region of neck, shoulder girdle and upper extremities.

Allergic skin lesions include urticaria, angioneurotic edema, generalized erythema, dis-

Table 6.1 : Commonly used barbiturates

Name	Preparation	Sedative (mg.) 3-4 times daily	Hypnotic single dose (mg.)
Long-acting			
Phenobarbitone I.P. (Gardenal, Luminal)	30, 60, 100mg. tab.	15-30	100-200
Phenobarbitone sodium	30, 60 mg. tab.	30	60 - 120
Phenobarbitone sodium (Gardenal inj.)	200 mg. inj.	-	60--200 I.M.-I.V.
Intermediate-acting			
Butobarbitone (Soneryl)	100 mg. tab.	30	100-200
Phenobarbitone sodium I.P. (Nembutal)	30, 50, 100 mg. capsules 50 mg/ml.inj.	30-50 -	100 50-100
Amylobarbitone Sodium I.P. (Amytal)	60 mg. tab.	30	100-300
Short-acting			
Secobarbitone sodium I.P. (Quinalbarbitone, Seconal, Shortal, Lipaton)	100 mg. tab. 4 mg./ml. elixir 250 mg. inj.	30	100-200

crete macules or generalized morbilliform rash. Pentobarbitone occasionally causes exfoliative dermatitis, which may be accompanied by hepatitis, agranulocytosis and thrombocytopenic purpura.

(b) Prolonged phenobarbitone therapy may produce megaloblastic anemia which responds to folic acid.

(c) Barbiturates, if administered to a woman during labour, may depress the foetal respiration.

(d) Barbiturate administration may precipitate an attack of acute intermittent hepatic porphyria.

(e) If a barbiturate is being employed as a hypnotic, because of confusion and amnesia, a patient may repeatedly take the barbiturate at night and poison himself. This phenomenon is known as 'drug automatism'.

(f) *Tolerance*: Tolerance usually develops on repeated administration of barbiturates. Tolerance can be attributed to (i) increased hepatic inactivation and (ii) adaptation of the nervous tissue to the drug. Barbiturate addicts often show cross tolerance to other general depressants of CNS including the volatile and general anaesthetics. *However, tolerance to the hypnotic effect of barbiturates fails to modify their lethal dose significantly.* Acquired barbiturate tolerance usually disappears completely within 1 to 2 weeks of abstinence.

(g) *Drug interactions*: Barbiturates, when combined with other C.N.S. depressants such as alcohol, benzodiazepines and antihistaminics may cause severe depression. Monoamine oxidase inhibitors also enhance the C.N.S. depressant effect of barbiturates. Hepatic induction caused by barbiturates reduces the effectiveness of many drugs as discussed earlier. The administration of phenobarbitone to asthmatics who are dependent on corticosteroids has been reported to exacerbate asthma.

(h) *Drug dependence*: Repeated administration of barbiturates causes drug dependence. The characteristic manifestations of chronic barbiturate intoxication are thick slurred speech, ataxia,

impaired superficial and deep reflexes, hypotonia, nystagmus and difficulty in accommodation. The nutrition is usually unimpaired. With the withdrawal of the barbiturate, there might be an apparent improvement during the first 12 to 16 hours. This is followed by anxiety, restlessness, tremors, abdominal cramps, nausea, vomiting, orthostatic hypotension and prostration. Convulsions with the withdrawal of short acting barbiturates usually develop on the 2nd or 3rd day of abstinence while they are manifested from 4th to 7th day in case of long acting barbiturates. Visual hallucinations, disorientation and delirium are the other serious manifestations which develop from 4th to 7th day and are accompanied by cardiovascular collapse. Usually the withdrawal syndrome is mild and clears up by about the 8th day but sometimes may last for many weeks.

Chronic barbiturate poisoning should be treated on the same lines as chronic alcohol intoxication. Although in mild cases the drug may be withdrawn suddenly, generally the withdrawal should be gradual, over 10 days to 3 weeks, depending upon the severity of the dependence. No specific drug is available for treatment of barbiturate addiction and the therapy is purely symptomatic. If desired, replacement could be made with a hypnotic like chloral hydrate 1 g., chlordiazepoxide 50 mg., or diazepam 10 mg.

Acute barbiturate poisoning: Acute barbiturate poisoning results from ingestion of an overdose either accidentally or with suicidal intent. The clinical picture is characterised by depression of the central nervous system, particularly the respiration and a peripheral circulatory collapse. The patient thus shows weak and rapid pulse, cold clammy skin and slow or rapid and shallow breathing. Cheyne-Stokes rhythm may be present. The pupils may be constricted and reacting to light initially but subsequently develop paralytic dilatation. The frequent and often fatal complications are respiratory (atelectasis, pulmonary edema and bronchopneumonia) or renal (acute renal shutdown).

Treatment of acute barbiturate poisoning : The severity of barbiturate poisoning is assessed by clinical signs prior to treatment and correlates well with plasma levels of barbiturate. Presence of reflexes, response to painful stimuli and maintenance of blood pressure and of respiration without external assistance indicate a fair prognosis, while cases showing deep coma with absent reflexes, respiratory depression and cardiovascular collapse have a high mortality.

The treatment consists of :

(a) **Gastric lavage :** If the patient is conscious and less than four hours have elapsed since ingestion, vomiting may be induced with syrup of ipecac or concentrated salt solution. If the patient is unconscious, simple aspiration of the gastric contents is helpful if carried out within four hours of barbiturate ingestion. Care should be exercised to prevent the aspiration of the contents into the respiratory passage. In comatose patients, endotracheal intubation with a cuffed tube should precede gastric intubation to prevent such aspiration.

(b) **Endotracheal intubation :** Adequate ventilation is of primary importance in the treatment of barbiturate intoxication. Cerebral anoxia enhances the depressant action of barbiturates and increases their penetration into the central nervous system. If the respiration is not much affected, oxygen can be given by a nasal catheter. Endotracheal intubation is performed when spontaneous respiration is inadequate and also to remove secretions in those patients who show depressed cough and pharyngeal reflexes. Positive pressure respiration should, therefore, be used to treat hypoventilation. Room air is preferable to high oxygen concentration as hypoxia may become the major respiratory stimulus after barbiturate depression and over correction of hypoxia by high concentration of oxygen may cause apnoea. If assisted ventilation is required for more than 24 hours, tracheostomy is usually performed. Frequent turning of the patient, tracheal suction and encouraging the patient to cough on awakening help to minimize respiratory complications.

Frequent monitoring of blood gases and blood pH, if available, is helpful. Respiratory physiotherapy minimizes lung complications.

(c) **Forced diuresis :** Hypotension and release of antidiuretic hormone reduce the urinary output in barbiturate intoxication. As the unbound circulating barbiturate is passively filtered at the glomerulus and as the nonionized form is passively reabsorbed along concentration gradients established in the tubule, barbiturate excretion can be enhanced considerably by increasing the urinary flow.

It must be noted that forced diuresis is a potentially dangerous procedure and should only be considered for those patients who have taken phenobarbitone in such doses that they are unlikely to survive with supportive therapy alone. Forced diuresis must not be used as a substitute for the intensive supportive therapy as outlined above as most of the deaths are because of failure to maintain adequate tissue oxygenation.

Diuretics like mannitol and furosemide have been employed to increase urinary elimination of barbiturates. Mannitol, an osmotic diuretic, is given intravenously, initially in the dose of 100-120 ml. of 25 per cent solution. Subsequently, a sustained infusion of 5 per cent mannitol alternately in a litre of normal saline and a litre of 5 per cent dextrose is administered at the rate of 500 ml. per hour for next 3 hours. The infusion is thereafter adjusted depending upon urine output and the state of hydration. Potassium chloride (10 to 20 mEq.) may be added to each litre according to serum chemistry and alkalization with sodium bicarbonate may be conveniently carried out through the drip. An average urine volume of 10-12 litres in 24 hours (a flow rate of 8-10 ml. per minute) is considered as satisfactory diuresis and this rate can be achieved by adequate hydration and osmotic diuretics. The dose of mannitol should not be more than 20 g. per hour. Forced diuresis is terminated on awakening of the patient.

If a more powerful diuretic is desired then furosemide (Lasix) is used in the dose of 20 mg. along with 500 ml. of 1.2 per cent sodium bicar-

bonate and one litre of 5 per cent dextrose, intravenously in the first hour. The urine flow should be above 5 ml. per minute at the end of the hour. If it is not, furosemide should be given intravenously in large doses (upto 500 mg. per 24 hours) but it is absolutely essential to monitor repeatedly the serum chemistry, central venous pressure and urine output.

Patients who do not respond to either mannitol or furosemide with adequate diuresis are likely to have impaired renal function and should be considered for dialysis.

Forced diuresis is most useful in poisoning due to phenobarbitone, barbitone and allobarbitone. It is not of much value in poisoning due to other barbiturates which are more protein bound, have a large volume of distribution and are less ionized at the achievable urine pH.

Shock, cardiac failure and renal impairment are absolute contraindications for forced diuresis. It should also be noted that almost all the patients subjected to forced diuresis develop potassium deficiency and this should be corrected.

(d) **Alkalinization** : Mild systemic alkalosis reduces the plasma concentration of the non-ionized and diffusible form of barbiturate and this leads to withdrawal of barbiturate from the brain and the cerebrospinal fluid. In addition, alkalization of urine prevents tubular reabsorption by ionization of the filtered barbiturate and thus enhances its elimination. Alkalinization of the urine produces a significant increase in the excretion of long acting barbiturates, particularly phenobarbitone; it has no significant effect on the renal elimination of short acting barbiturates because of their poor ionization even in alkaline medium and their high lipoid solubility. Sodium bicarbonate 3.5 g. per 50 ml. (45 mEq.) may be added to every litre of fluid intended for intravenous administration. The urinary pH should be checked hourly and maintained between 7.5 and 8.5.

Another substance advocated for combating metabolic acidosis is THAM [tris (hydrox-

ymethyl) aminomethane]. This compound combines with carbon dioxide and water to form bicarbonate and a cationic buffer. It is administered intravenously as a 1/3rd molar solution in 0.2 per cent sodium chloride. However, the drug itself may depress the respiratory centre directly and also produces hypoglycemia.

(e) **Prophylactic antibiotics** : These should not be used routinely. Only in severe cases, especially those requiring tracheostomy or catheterization of urinary bladder, they may help in preventing infection.

(f) **Intravenous fluids** : Fluids must be given in sufficient quantity as an adjuvant to forced diuresis, in order to prevent dehydration. They are also indispensable for maintaining the blood volume in the treatment of vasomotor shock. Normal saline with dextrose is employed for this purpose. If hypotension does not respond to replacement by fluids vasopressor agents like dopamine may be used (see shock, Chapter 28). It must be emphasized that overloading of the circulation should be avoided.

(g) **Dialysis** : Elimination of barbiturate from the body can be hastened by peritoneal dialysis and by hemodialysis. Both are more effective in removing long acting barbiturates than in removing short acting ones. In general, peritoneal dialysis is not more effective than forced diuresis in promoting elimination of a barbiturate but is more suitable than the latter in patients who have severe renal impairment and in those in whom the cardiac status precludes vigorous fluid administration. Hemodialysis is about forty times more effective than forced diuresis in promoting barbiturate elimination. It is especially indicated in the following situations : shock; progressive deterioration with conservative therapy; ingestion of a potentially lethal dose; finding of potentially lethal blood levels; and in patients in whom peritoneal dialysis is ineffective or contraindicated. Charcoal hemoperfusion is now considered superior to peritoneal dialysis and hemodialysis in this therapy.

(b) Related ureides :

GLUTETHIMIDE (Doriden) : Glutethimide is administered orally as a daytime sedative and as a hypnotic in the dose of 125 mg. 3 to 4 times daily and 0.5 to 1 g. at bedtime, respectively. The drug is erratically absorbed from the gastrointestinal tract and is almost completely metabolized in the body. Hypnotic effect starts in about 30 minutes, and is long lasting.

Hyper-reflexia, intermittent spasticity and muscular twitchings, respiratory depression, hypotension, mydriasis, paralytic ileus and dryness of mouth are the prominent features of acute intoxication. Blood dyscrasias, peripheral neuritis and toxic psychosis may develop. The drug is capable of inducing dependence. The drug appears to have no advantages over barbiturates.

METHYPRYLONE (Noludar) : This drug is chemically related to glutethimide and has hypnotic and addictive properties and adverse reactions similar to those of barbiturates. In the dose of 50-100 mg. 3 to 4 times a day, it is used as a daytime sedative. Its hypnotic dose is 200-400 mg. at bed time.

BENZODIAZEPINES

BENZODIAZEPINES : These compounds are used as antianxiety agents and are described in Chapter 11. Their hypnotic property is discussed here.

All benzodiazepines have a hypnotic action. Diazepam (5-10 mg), flurazepam (15-30 mg.) and nitrazepam (5-10 mg.) have proved highly effective hypnotics. The benzodiazepines cause sedation, hypnosis, decreased anxiety, muscle relaxation and some of them also possess anticonvulsant activity. These drugs affect activity at all levels of the neuraxis, though some structures are affected more than others. In contrast to barbiturates, they do not cause true anaesthesia. All benzodiazepines are qualitatively similar in their effects on the important sleep parameters. They shorten the time spent in stage 4 and REM sleep, but increase the

total sleep time. Clinically, sleep induced by benzodiazepines is more refreshing with less hangover than that following a barbiturate. Further, in therapeutic doses these drugs do not produce any significant action on respiration, gut and cardiovascular system. Tolerance to benzodiazepines can occur and discontinuation after prolonged use may give rise to rebound symptoms associated with increase in REM sleep time. However, as compared to barbiturates, benzodiazepines probably preserve near normal sleep pattern, exhibit less REM rebound after withdrawal and remain effective for longer periods of administration. Further, the therapeutic index appears to be high and there are less chances of causing unconsciousness and marked respiratory depression following overdosage.

Benzodiazepines are relatively less toxic. Because of these distinct advantages, they are now preferred to barbiturates as hypnotics.

The benzodiazepines are adequately absorbed when given orally; but, their pharmacokinetic properties differ considerably. The bioavailability differs with different benzodiazepines. The extent of protein binding also varies. Hence the duration of action differs significantly. Thus, flurazepam (half life 24 - 100 hr) and diazepam (half life 20 - 90 hr.) are longer acting than nitrazepam (half life 18 - 34 hr) and lorazepam (half life 10 - 20 hr.). Oxazolam and triazolam have half lives of less than 4 - 5 hours (see Chapter 11). Moreover, chlordiazepoxide and diazepam show a linear, age related increase in elimination half-life. Hence, benzodiazepines like oxazolam and lorazepam with short half-lives and lack of active metabolites are preferred in the elderly.

ALCOHOLS

ETHANOL: Taken at bedtime, ethyl alcohol may act as a mild sedative. However, it cannot be recommended as a hypnotic as in small doses it may produce excitement. In addition, there is the danger of drug dependence.

CHLORAL HYDRATE AND TRICHLOROETHANOL: Chloral hydrate is a white crystalline substance, readily soluble in water. In the body, it is converted to a significant extent into trichloroethanol.

Applied locally, it acts as a rubefacient and is incorporated in liniments such as camphorated chloral.

The principal effect of chloral hydrate in small doses is sedation. A slightly larger dose (1 g.) at bed time results in sleep. On oral administration, sleep is induced within 1 hour and continues for 4 to 5 hours or longer. The drug facilitates the sleep induction, but does not affect sleep maintenance significantly. The patient can be easily aroused from sleep and the respiration and blood pressure are not much affected. It does not significantly alter normal sleep pattern. From the practical point of view, it is a rapidly effective, reasonably safe, and cheap hypnotic drug.

A sedative dose of chloral hydrate does not exert any significant anticonvulsant, analgesic, antitussive or antiemetic effect.

Absorption, fate and excretion: Chloral hydrate is satisfactorily absorbed from the gastrointestinal tract including the rectum. A part of the compound is oxidized to trichloroacetic acid in the liver and the kidney, the reaction being catalysed by the enzyme alcohol dehydrogenase. Trichloroacetic acid does not possess any hypnotic activity. Its urinary excretion, however, is very slow. The remainder of the drug is probably reduced to trichloroethanol which possesses hypnotic activity. The hypnotic activity of chloral hydrate is at least partly due to its reduction to trichloroethanol. The latter is mainly conjugated with glucuronic acid and excreted in the urine as urochloralic acid while a part of it may be converted to trichloroacetic acid. Urochloralic acid decomposes in an alkaline medium and the products give a false positive Benedict's test. The conversion of chloral hydrate to trichloroethanol occurs in all the tissues including the brain and blood.

Adverse reactions : The commonest adverse

reaction is allergic skin rashes.

It has an unpleasant taste, and may produce nausea and vomiting due to irritation of the gastric mucosa. It should be given well diluted, preferably in fruit juice. Hangover may occur. In therapeutic doses, it may produce delirium and excitement in the presence of pain.

Toxic doses (more than 10 g.) cause loss of reflexes, pinpoint pupils and depression of the vasomotor and respiratory centres. Large doses also cause myocardial depression or cardiac arrhythmias. Jaundice and albuminuria may appear as late sequelae because of hepatic and renal damage.

Tolerance and drug dependence are rare. In an addict, a 'break' in tolerance may result in death; abrupt withdrawal of the drug may result in delirium, mania and convulsions.

Chloral hydrate produces an additive effect with ethyl alcohol.

Preparations:

(a) Chloral hydrate is administered usually as a mixture in the dose of 0.5 to 2.0 g. In children it is given as a syrup in the dose of 125 mg. per year of age to a maximum of 375 mg. Infants may be given 50 to 75 mg. per dose.

(b) Trichloroethyl phosphate (Trichloryl): This is the sodium salt of the phosphoric acid ester of trichloroethanol. It probably causes less gastric irritation. It is supplied as a syrup containing 0.5 g./5 ml. and 0.5 g. tablet

Contraindications: The drug should be avoided in the presence of marked hepatic, cardiac or renal damage, peptic ulcer, oesophagitis and gastritis.

ALDEHYDES

PARALDEHYDE : Paraldehyde is a colourless, transparent and inflammable (but not explosive) liquid with a characteristic odour and an acid taste.

Paraldehyde is usually given by rectal or intramuscular route to induce hypnosis. When given orally, sleep is induced within 15 to 30 minutes

and lasts for 6 to 8 hours. Hangover is uncommon. Therapeutic doses of paraldehyde have no deleterious effects on the respiratory and the vasomotor centres. Administered during labour, it may exert a mild analgesic effect. However, it crosses the placental barrier and may delay the establishment of breathing in the newborn. Paraldehyde is a useful anticonvulsant. The drug is mainly metabolised in the liver. About 11-28 per cent is excreted unchanged through the lung and only 0.1-2.5 per cent through the kidney.

Adverse reactions: Paraldehyde is irritant to the rectal and gastric mucosa. It may produce tissue necrosis and nerve damage on intramuscular administration. The drug decomposes to acetic acid and acetaldehyde in the presence of light and heat and death may result from administration of old paraldehyde. *Hence, paraldehyde kept for more than 6 months should not be used.*

Even though paraldehyde is claimed to have a weak analgesic activity, it may produce excitement and delirium in the presence of pain. It is excreted in breath to a significant extent and imparts odour to breath which may worry the patient and annoy others.

Acute paraldehyde poisoning is characterized by hypotension, respiratory depression and coma. The degradation products of paraldehyde may produce pulmonary haemorrhage and edema. Severe metabolic acidosis, hepatotoxicity and nephrotoxicity are often noted.

Tolerance and addiction to paraldehyde may develop. Alcoholics exhibit cross tolerance to paraldehyde. *It can dissolve many plastic articles and hence cannot be injected by a plastic syringe.*

Preparations and dosage:

(a) Inj. paraldehyde I.P. 5 to 10 ml. administered deep intramuscularly in the buttocks. When a dose of 10 ml. is being administered, it is advisable to divide it in between two sites to minimize local irritation. The drug does not support the growth of micro-organisms and may be used as such in an emergency.

(b) It can also be given rectally in the dose of 15-30 ml. after suitable dilution.

Therapeutic uses :

(a) As an anticonvulsant in status epilepticus, tetanus and eclampsia, usually by intramuscular route. Its intravenous use is not recommended as it may cause violent coughing and pulmonary edema.

(b) As a hypnotic, it is rarely used.

Contraindications: The drug should not be administered orally or per rectum in patients with inflammatory lesions of the gastrointestinal tract. In patient taking disulfiram, a syndrome akin to that seen after alcohol ingestion may develop. It should be avoided in the presence of severe impairment of the hepatic and pulmonary function.

ACETYLATED CARBINOLS

ETHINAMATE (Valmid) : Ethinamate, a drug administered orally in the dose of 0.5 g. to elicit hypnotic effect, is claimed to have a duration of action about half that of pentobarbitone. The drug is mainly detoxified in the liver. It does not seem to have any significant advantage over barbiturates.

MISCELLANEOUS AGENTS

METHAQUALONE (Melsedin) : This drug is no more used as a hypnotic because of its extensive misuse as a drug of addiction.

Certain antihistaminics like diphenhydramine and promethazine have potent hypnotic activity. These drugs are sometimes preferred to barbiturates in paediatric practice as children are more susceptible to barbiturate depression. The parasympathetic blocking agent scopolamine has a mild sedative activity; it is not commonly employed as a hypnotic because of its peripheral parasympathetic blocking actions.

Antianxiety drugs such as meprobamate also have a sedative-hypnotic action resembling that of barbiturates. Antidepressant tricyclic compounds and MAOI also alter sleep in normal subjects and in patients suffering from depression (see Chapters 11 and 20).

INORGANIC IONS

BROMIDES : With the advent of better therapeutic agents the use of bromides as hypnotics is obsolete. (See earlier editions.)

PHARMACOTHERAPY OF INSOMNIA
AND OTHER SLEEP DISORDERS

Ability to go to sleep is a very personal attribute and people are either 'good sleepers' or 'poor sleepers'. The latter, on the whole, take longer to fall asleep, sleep less, awaken more, have less REM and stage 4 NREM sleep, and have higher physiological arousal (heart rate, body temperature) than good sleepers. At the extreme end of the spectrum of poor sleepers is the person who sleeps through the whole night in several cat naps instead of sleeping continuously. As with all other things in life, most people learn to live with their own sleeping pattern.

Insomnia is said to be present when an individual *complains* of inability to fall or stay asleep, or reduction in the total sleep period, of sleep disturbed by nightmares or of sleep that does not refresh. Transient (no more than a few nights) and short-term insomnia (less than about 3 weeks) may occur in the absence of disease and is then due to stresses caused by reactions to life changes such as environmental factors, job requirements, travelling through time zones etc. Other than this, insomnia may be due to physical discomfort such as pain, dyspnoea, fever or psychiatric causes such as anxiety. It may occasionally be induced by inappropriate or excessive use of central stimulant drugs such as ephedrine, amphetamine and of caffeine containing beverages.

Chronic insomnia by definition lasts for at least 3 weeks and needs detailed evaluation. A two week sleep diary and an interview with the sleep-partner may be useful. Between 1/3 to 2/3 of the patients with chronic insomnia have a recognizable psychiatric illness such as depression, psychosis etc.

If insomnia is due to severe pain, opioid analgesics (opiates and their substitutes) are obviously

the drugs of choice. If pain from joints, integumental structures, headache or toothache is keeping the individual awake, analgesic antipyretics (salicylates and related drugs) are preferred. It is imperative to ascertain whether any organic cause is responsible for insomnia and attempts should be made to treat the cause whenever possible. Sudden fearful awakening with palpitation and sweating should arouse the suspicion of an associated major disorder such as angina, hypoglycemia or severe anxiety state. The presence of dyspnoea in such a patient may indicate early heart failure which should be ruled out before a hypnotic is prescribed.

Sometimes, insomnia due to mental disturbances needs appropriate psychiatric evaluation. Difficulty in staying asleep is a frequent complaint of depressed patients. This is associated with marked decrease in stage 4 of NREM sleep. It is unlikely to be benefited by hypnotics, and treatment of depression is of prime importance.

In cases with "primary" insomnia, certain simple measures help the patients to improve the sleep. Patients should avoid day naps and should be encouraged to take moderate exercise several hours before bedtime; this has been shown to increase stage 4 NREM sleep. Patients should be advised to establish a regular bedtime hour and to condition themselves to going to bed only when sleepy; they should not remain in bed if they cannot sleep. All complex mental activities such as studies should be avoided prior to bedtime and some fill up for the stomach such as a glass of warm milk would be useful. Milk is known to contain tryptophan and d-tryptophan is known to reduce the time of onset of sleep in volunteers. Training in relaxation and yoga or meditation may also be helpful. With these suggestions, drugs can be used with greater effectiveness.

As insomnia can be troublesome to the sufferer, if the above mentioned simple measures fail to rapidly restore the normal sleeping pattern, there should be no hesitation in using 'hypnotic' drugs. Pharmacologically, it is impossible to clearly separate sedative, antianxiety and hypnotic drugs. It would appear that with most drugs

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belonging to these classes, the desired effect can be produced by an appropriately adjusted dose.

In therapeutic doses, most 'hypnotic' drugs have similar actions in decreasing the latent period of sleep, increasing the total sleep time, decreasing the awake time and awakenings, increasing the duration of stage 3-4 NREM sleep and reducing the REM sleep. There are more similarities than differences among these drugs. The differences are, however, of practical importance and depend upon (1) rapidity, (2) duration of action, (3) differences in the degree of suppression of REM sleep and (4) adverse reactions especially liability to produce dependence.

If a person has difficulty in falling asleep, a drug that is rapidly effective such as diazepam 5-10 mg or 1 g. of chloral hydrate should be administered 20 minutes before the usual bedtime. For persons with difficulty in maintenance of sleep, longer acting drugs like chlordiazepoxide may be preferred. For persons who find it difficult to sleep initially and also to maintain the sleep, diazepam 10 mg may be useful. Chloral hydrate is better avoided in the presence of peptic ulcer because of its irritating nature.

Most hypnotic drugs like secobarbitone, pentobarbitone, glutethimide, and the antihistaminic diphenhydramine tend to reduce REM sleep. Many antidepressant drugs are powerful in suppressing the signs of this phase of sleep. Since it has been demonstrated that in patients with duodenal ulcer, marked increase in gastric acid secretion frequently occurs during REM sleep and that episodes of nocturnal angina are associated with REM sleep, its suppression may be useful in such patients. In such cases, treatment once started should not be withdrawn suddenly for the fear of 'rebound' reaction, which could worsen the condition. Sudden withdrawal of REM suppressants causes a sharp increase in the REM sleep. Such a 'rebound' in an anxious patient is often associated with increased dreaming, nightmares, restlessness, insomnia and even fits. In its most severe form, the withdrawal state is one of delirium tremens with terror and marked insomnia. Some

patients may, therefore, continue the drug to avoid these reactions, thus leading to drug dependence. Eventually, a chronic state of intoxication ensues with tremor and confusion during day and insomnia at night.

Whatever 'hypnotic' drug is chosen, it should be used initially in a small dose which should be increased only if absolutely necessary. Once a good night's sleep is obtained, attempts should be made to omit the drug for a few nights. The drug should be used to condition the patient to sleep better and should not be allowed to make a slave out of him. He should be explained that he can now sleep well without the drug and that an occasional night of imperfect sleep will not harm him.

Unlike the drugs mentioned above, antipsychotic phenothiazine derivatives are poor hypnotics. It is, therefore, rational to prescribe a conventional hypnotic to treat uncorrected insomnia in a patient on antipsychotic drugs.

The important drawback of all hypnotics is the 'hangover'. All of them impair the performance the next day, even in recommended therapeutic doses. Even smaller amounts used as daytime sedative can impair social judgement and performance. Impairment of performance and persistent EEG changes have been shown to continue for a considerable time after a single dose of barbiturate although the hypnotic effect is over and the subject may appear apparently alert. Patients should be, therefore, warned not only about the possible interactions of hypnotics with alcohol and other drugs, but also about the possibility of impaired performance such as car driving the next day.

It is highly unlikely that a potent hypnotic will not cause hangover and will be free from tolerance and dependence liabilities. However, the benzodiazepines are safer than barbiturates in that it is difficult to commit suicide with them. Benzodiazepines also interfere less with R.E.M. sleep and the normal sleep cycle. Further, rapid development of tolerance is a distinct disadvantage of barbiturates. Hence, *benzodiazepines are now the*

drugs of choice as hypnotics.

Often a patient taking hypnotics also takes other drugs simultaneously. Such combinations can be sometimes dangerous. Thus, MAO inhibitors taken to relieve depression may lead to slow inactivation of other depressant drugs, giving rise to serious toxicity in otherwise nontoxic doses.

Sedatives and hypnotics are indicated in various situations in children but they should not be employed as a substitute for other important measures such as discussion with the parents about their children's behavioural problems and the importance of change in parental attitudes. Chloral hydrate 60 mg. or phenobarbitone 15 mg. given 2-3 times a day can act as a good daytime sedative in infants. For sleep problems in adults, chloral hydrate in doses of 500 mg. is highly effective and safe. Routine use of barbiturates and other drugs for things like tics, nightmares, breath-holding attacks, masturbation, aggressiveness, fears and school phobias, and head banging is not considered justifiable. The more rational approach in all these cases is to discuss the psychological problem with the mother.

Sleepwalking and *night terror* are the mild and severe manifestations of the same disorder occurring about 1-3 hours after the onset of sleep, when stage 3 and 4 sleep is more prevalent. The disorders are idiopathic when they begin in childhood and benefit from (a) safety precautions and (b) the use of drugs like diazepam and flurazepam which suppress stages 3 and 4 of sleep. An organic cause such as a brain tumour must be ruled out when they have their onset in adult life.

Nightmares, commonly known as bad dreams, occur during REM sleep. They may occur in normal children and in children with fever. The best way to handle them is to avoid terrifying stories, movies and frightening T.V. programmes. When they occur for the first time in adult life, depression is an important cause, and such depressed patients may be at increased risk for suicide.

Very often, a clinician is tempted to prescribe a hypnotic drug readily under pressures--from

patients, relatives, nursing staff or even himself. In the long run, this attitude may cause more harm to the patient than good. It is useful to remember that :

- (1) periodic loss of sleep in itself is not harmful and therefore, does not require treatment with drugs. Many professionals like doctors, nurses and seamen who regularly lose sleep throughout their career remain resilient, healthy and hardworking;
- (2) the clinician should not have a negative approach to what lies behind the presented symptom of sleeplessness and hypnotics must not be prescribed readily '*on demand*';
- (3) one should be more critical in repeating the '*sleeping pill*' prescription and try to avoid its continuation;
- (4) no hypnotic is safe, all can cause harm and none is effective in helping patients with the problems underlying their insomnia; moreover many of these drugs lose their effectiveness on repeated administration. Special caution is necessary in patients with respiratory diseases, suicidal tendencies and drug dependence. The risk of falls and fractures increases in patients using hypnotics and other psychotherapeutic agents.
- (5) the difficulties of stopping the hypnotic in chronic hypnotic users could be enormous. Lastly,
- (6) we still do not know the specific importance of sleep stages and their lengthening or shortening following hypnotics. Hence, effectiveness and safety are still the main considerations in prescribing hypnotic drugs.

In practice, it suffices to know properly a few well tried hypnotics such as benzodiazepines, chloral hydrate and sometimes phenobarbitone. A patient with mental depression needs a tricyclic antidepressant such as imipramine.

REQUIREMENTS OF AN IDEAL HYPNOTIC

(a) The drug should be effective orally quickly, with a predictable and sufficiently long hypnotic action. The sleep induced should resemble natural sleep.

(b) It should be non-irritating, non-toxic and should not produce hangover.

(c) Tolerance, habituation and addiction must not develop.

(d) It should be cheap and

(e) There should be little danger of successful suicide if an overdose is taken.

7 Drugs Effective in Convulsive Disorders

Drugs used in the treatment of convulsive disorders (anticonvulsants) can be divided into :

I. Drugs which are used to abolish convulsions and II. Drugs which are administered prophylactically to prevent the occurrence of convulsions. This group of drugs includes antiepileptics.

Majority of anticonvulsants are nonspecific depressants of the central nervous system. However, the converse is not necessarily true. Thus, morphine, reserpine and chlorpromazine do not abolish convulsions. Anticonvulsant drugs can be classified as :

(a) Centrally acting e.g. general anaesthetics, paraldehyde, barbiturates and diazepam.

(b) Acting mainly on the spinal cord e.g. mephenesin (See Chapter 18).

(c) Peripheral skeletal muscle relaxants e.g. d-tubocurarine and succinylcholine (See Chapter 18).

Experimental methods for evaluating antiepileptic drugs : Drugs with a potential antiepileptic activity are assessed against convulsions induced in mice by injecting medullary stimulants or by applying a maximal electrical shock. The chemical commonly used to produce convulsions is pentylenetetrazol (leptazol). It is usually injected subcutaneously as 1 per cent solution in the dose of 100 mg. per kg. body weight. Drugs which antagonize leptazol convulsions are usually useful in petit mal.

For inducing convulsions by electrical shock, a rectangular pulse current of high voltage (140 volts AC), is usually employed. Drugs likely to be effective in grand mal epilepsy usually confer

protection against electrically induced convulsions in animals. For testing a potential antipsychomotor-epilepsy drug, the unidirectional current of low frequency is used to produce automation in animals.

The anticonvulsants can also be evaluated against convulsions in larger animals. Thus, talc or alumina cream applied directly to the cortex of a monkey can act as a source of chronic irritation and injection of any corticomedullary stimulant can then precipitate convulsions in such an animal. Such a focus can also give rise to secondary epileptogenic foci in distant areas of the brain.

A more recent model for human focal epilepsy is that produced in animals by "Kindling". This consists of delivery of brief localized trains of electrical stimuli to an area of the brain, repeatedly, at about 24 hour intervals. After a time, generalized motor seizures are regularly elicited during such electrical stimulation. Although spontaneous, recurring seizures are not produced, such 'kindled' animals are very sensitive to a variety of chemical and sensory convulsive stimuli.

PHARMACOTHERAPY OF EPILEPSY

Epilepsy is a collective term for a group of chronic seizure disorders having in common, sudden and transient episodes (seizures) of loss or disturbance of consciousness, usually but not always with a characteristic body movement (convulsions) and sometimes with autonomic hyperactivity. The seizure nearly always correlates with an abnormal E.E.G. discharge.

Epileptic seizures can be classified into :

(A) Primarily generalized seizures

- (1) *Tonic - Clonic seizures* are generalized from their earliest manifestations and are accompanied by a generalized abnormality in the EEG. (*Grand - mal or major epilepsy*). This is characterized by sudden loss of consciousness without any warning (aura), followed by generalized tonic, followed by clonic convulsive movements. This is followed by a period of headache, drowsiness, confusion and sleep. The attack may be accompanied by tongue biting, frothing at the mouth and incontinence.
- (2) *Tonic seizure* : As above but without clonic phase. The postictal phenomena are usually less severe.
- (3) *Clonic seizure* : As (1) above but without the tonic phase. The postictal phase usually lasts for a short time.
- (4) *Absence seizure (Petit - mal)* : It consists of sudden cessation of ongoing conscious activity without convulsive movement and without loss of postural control. The patient appears to go blank for one second to one minute, and there may be accompanying fluttering of eyelids or small chewing movement of the mouth. Awareness of the surroundings is regained quickly at the end of an attack, and the patient may not even know that one has occurred. The E.E.G. is diagnostic with diffuse, bilaterally synchronous 3 per second wave and spike discharges. Absence seizures almost always begin in childhood and are idiopathic in origin. The child may outgrow these seizures or may continue to have them in adult life. Some children have additional generalized tonic-clonic seizures. Typical absence seizures respond well to drug treatment. In children with underlying brain disease, absence seizures may co-exist with other types of generalized seizures and then are resistant to drug treatment.

(5) *Atonic seizure (Drop attack)* : Such a seizure consists of sudden loss of consciousness and of postural tone, without accompanying tonic or clonic movements. The individual simply drops to the floor without any apparent cause. There are other causes of drop attacks than epilepsy.

(6) *Myoclonic seizure* : This is a sudden, brief, repetitive muscle contraction involving one body part or the whole body. In the latter case, there is a violent fall without loss of consciousness. Myoclonic seizures may occur by themselves or coexist with other types of seizures. They may be idiopathic or may be due to other neurological conditions. The E.E.G. changes are characteristic.

(B) Partial seizures are always due to a focal brain lesion, and there is an E.E.G. focus of abnormality which may or may not become generalized.

(1) **Simple partial seizures** : There is no impairment of consciousness, and a wide range of clinical phenomena may occur depending on the site of the brain lesion.

(a) *Motor* : This begins as recurrent contractions of a part of the body and may spread to involve contiguous areas.

(b) *Sensory* with numbness or paraesthesia limited to one part of the body.

(c) Olfactory, gustatory, auditory and vertiginous symptoms.

(d) *Psychic symptoms* such as déjà-vu and dreamy states or unwarranted sense of fear or anger.

(2) **Complex partial (Psychomotor or temporal lobe epilepsy)** : These consist of an aura (unusual smell, sudden intense emotional feelings), followed by loss of contact with the environment. There may be simple motor activity such as lip smacking, swallowing or aimless wan-

dering or unconscious performance of highly skilled activities such as car-driving. There is amnesia for the entire period of the seizure. The E.E.G. shows a temporal lobe focus.

- (3) **Secondarily generalized seizures** (*cortical focal epilepsy, Jacksonian epilepsy*): This starts focally and develops into one of the generalized seizures listed above under (A). Such a seizure may be followed by postictal neurological deficit (Todd's paralysis). When the motor phenomena shows an orderly march, the seizure is called a Jacksonian seizure.

- (C) **Status epilepticus**: Prolonged or repetitive seizures (of any variety) without recovery between attacks comprises status epilepticus. When tonic-clonic seizures go into status epilepticus, the situation can be life threatening and is a medical emergency (see later).

Neurophysiology: John Hughlings Jackson postulated about a century ago that epileptic seizures were caused by "occasional, sudden, excessive, rapid, local discharges of grey matter". Modern electrophysiology has amply confirmed this. The characteristic pathophysiologic event in a seizure is believed to be paroxysmal depolarization shift of neuronal membrane potential and associated burst discharge. Excitatory neurotransmitters such as aspartate and glutamate are thought to be involved in the initiation and spread of the seizure discharge, and the inhibitory transmitter gamma-aminobutyric acid (GABA) is believed to be responsible for termination of the seizure activity. The underlying neurochemical defect in epilepsy may be a functional impairment in the inhibitory GABA mechanism. Benzodiazepines, sodium valproate, barbiturates and possibly phenytoin are now believed to work, at least in part, by enhancing GABA mediated inhibition. The normal brain contains billions of neurons which 'fire' asynchronously (i.e. at different

times). Inhibitory feedback loops in the normal brain regulate the frequency of firing of individual neurons and prevent synchronization. When such inhibitory feedback is defective, a large number of cells in a given area of the brain fire at the same time (i.e. they synchronize) and produce a self-regenerative electrical impulse. Such an area constitutes an *epileptic focus*.

Such foci may be cortical or subcortical. They may discharge intermittently only to be shown up on the gross, surface E.E.G. but not cause symptoms because their spread is blocked by the normal inhibitory mechanisms in the surrounding brain tissue. Factors which themselves cannot initiate seizures may trigger off the abnormal focus or permit the spread of activity to the normal brain. Such factors include alkalosis, hypoglycemia, overhydration, hypocalcemia, overeating, strong emotional states such as fright or embarrassment, various stages of sleep, intake of alcohol and rapid blinking of eyes or other rhythmic photic stimulation. Spread of the abnormal electrical activity to the normal brain tissue causes a generalized seizure. Such abnormal foci occur as a result of a demonstrable pathology but more often in its absence. The clinical type of seizure is independent of the brain pathology but is determined by the site of the abnormal focus and by the path taken by the seizure discharge. The response to treatment correlates best with the site of the epileptogenic focus.

Classification of anti-epileptic drugs

- I. **Hydantoin derivatives**: Phenytoin, methoin, ethosin.
- II. **Barbiturates**: Phenobarbitone, methylphenobarbitone or mephobarbitone, metharbitone and primidone.
- III. **Iminostilbenes**: Carbamazepine.
- IV. **Succinimides**: Phensuximide, ethosuximide, methsuximide.
- V. **Sodium valproate**.
- VI. **Oxazolidinediones**: Trimethadione, paramethadione.
- VII. **Benzodiazepines**: Clonazepam,

diazepam.

VIII. Miscellaneous : Bromides, acetazolamide, sulthiame, phenacemide, pheneturide and amphetamine.

I. Hydantoin derivatives :

DIPHENYLHYDANTOIN (Phenytoin sodium, Dilantin, Eptoin) : This drug was intro-

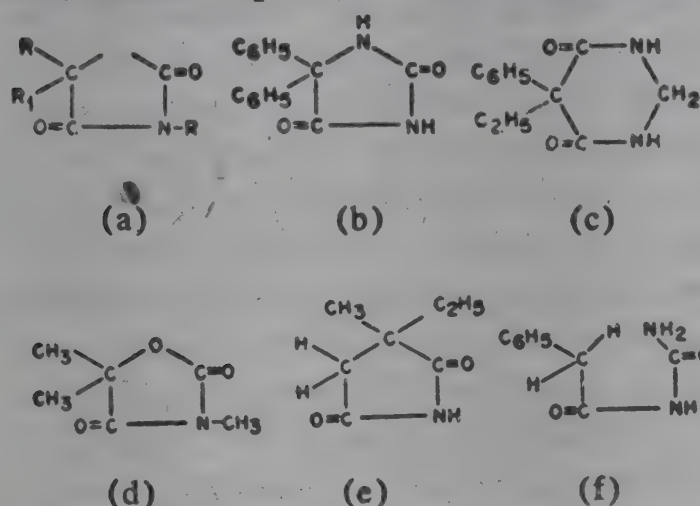


Fig. 7.1 : Antiepileptic drugs. The structures have been drawn to show similarities in different compounds.

(a) Basic structure associated with anti-convulsant activity. (b) Diphenylhydantoin. (c) Primidone. (d) Troxidone. (e) Ethosuximide. (f) Phenacemide.

duced in therapy by Merritt and Putnam in 1938. It is the primary drug in the treatment of epileptic seizures with the exception of petit mal.

Pharmacological actions : It exerts a selective antiepileptic action without causing drowsiness. The onset of action is slow even on intravenous injection but the action persists for a considerable time after cessation of therapy. This is thought to be due to a firm binding of the drug to the nervous tissue.

The exact mode of action of this drug is not known. Probably, it inhibits the spread of seizure discharges in the brain and shortens the duration of after-discharge. In patients in whom it is effective, the generalized abnormality in E.E.G. disappears but the abnormal focal electrical activity persists. Unlike phenobarbitone, the drug fails to produce a significant alteration in the electroshock seizures threshold in normal animals. The threshold may, however, be elevated to a moder-

ate extent after prolonged therapy. The drug has no protective effect against leptazol induced convulsions in animals.

The drug is known to decrease the neuronal sodium concentration leading to a reduction in the post-tetanic potentiation (P.T.P.) and to increase the neuronal potassium concentration. P.T.P. is an enhancement of synaptic transmission following repeated tetanic, high frequency stimulation of the presynaptic fibres. The cause of this phenomenon is not definitely understood but if an epileptic focus is visualised as a source producing high frequency tetanic impulses, the role of P.T.P. in the spread of seizures can be understood. Thus, enhancement of synaptic transmission due to P.T.P. may produce transmission of tetanic impulses, along the cerebral excitatory feed back circuits and the spread of such an activity across the entire brain would result in generalised grand mal seizures. Reduction in P.T.P. by phenytoin blocks this process and stops the spread of the seizure discharge. The work of Woodbury and associates indicates that the 'stabilising effect' of phenytoin is closely related to its ability to decrease the intraneuronal sodium concentration. P.T.P. is probably not involved in the genesis of petit mal epilepsy and the drug is consequently not effective in that condition. The drug has a stabilizing effect on all neuronal membranes including the peripheral nerve membrane as well as on all non-excitabile and excitable membranes. Phenytoin also augments brain level of GABA as well as 5HT and homovanillic acid. The restoration of a balance between the excitatory glutamate and inhibitory GABA (gamma amino butyric acid) pathways by phenytoin might be contributory to its antiepileptic action.

For actions on heart, see Chapter 25.

Absorption, fate and excretion : Phenytoin is slowly and variably absorbed from the gut and its peak in the plasma occurs 3-12 hours after ingestion. It is metabolized mainly by parahydroxylation of one of its phenyl rings in the liver. In plasma, it is 70-95% protein bound. The drug is concentrated in bile and reabsorbed from the intestine as parahydroxyphenol. Some indi-

viduals are deficient in the liver enzyme which ~~para~~hydroxylates this drug and in such individuals, toxicity is likely to occur even with small doses. It is excreted in urine and in saliva. At plasma concentration below 10 µg/ml, elimination is exponential and the plasma $t/2$ is about 24 hours; the variation in $t/2$ is four fold. At higher concentrations, it exhibits dose-dependent elimination. Hence, the plasma concentration rises disproportionately as the dosage is increased. About 94 per cent of a single dose is excreted in urine within 48 hours. On chronic medication, the drug disappears from the plasma within 3 days after discontinuation of treatment.

Adverse reactions : Such reactions are generally mild and only rarely do they enforce a cessation of therapy. Plasma levels of over 20 µg/ml are generally associated with adverse reactions. However, deaths are rare. Phenytoin is a poor drug for committing suicide.

At certain dosage levels, even a small increase in the dose may quickly lead to severe toxic symptoms. But they disappear equally quickly on reducing the daily dose by even a single capsule or tablet.

(a) **Intolerance :** Urticarial, scarlatiniform and measles-like skin rashes may occur, more frequently in children and in young adults. Hypertrichosis and hirsutism related to increased adrenocortical activity sometimes occurs in females. The skin reactions may be accompanied by lymphadenopathy, hepatomegaly and jaundice.

(b) **Central nervous system :** A vestibulocerebellar syndrome characterised by vertigo, ataxia, nystagmus and dysarthria is sometimes encountered during phenytoin therapy. Other effects like drowsiness, fatigue, headache and confusion, are occasionally observed. Ocular pain with blurring of vision, delusions, hallucinations and other psychotic episodes are sometimes encountered. Rarely, behavioural changes and even increased frequency of seizures may be seen. Peripheral neuropathy has been reported in old people receiving large doses for many years.

These effects are dose related and usually disappear within one to two weeks after the drug has been discontinued or the dose reduced to the tolerated level. Ataxia, however, may occasionally persist for as long as 6 months after drug withdrawal.

(c) **Gastrointestinal tract :** Gastric irritation, resulting in nausea and vomiting caused by the alkalinity of the drug, can be prevented by taking the total daily dose in divided portions, after meals, with plenty of fluids.

(d) **Gums :** Hyperplasia and hypertrophy of the gums with edema and bleeding occur in approximately 15 per cent of patients. These changes are not related to vitamin C deficiency. Gingival hyperplasia is commoner in children than in adults. The occurrence or degree of gingival hyperplasia is not related to the dose of phenytoin. In most cases, the gums return to normal within a year after discontinuation of the drug.

(e) **Miscellaneous :** Megaloblastic anemia responding to folic acid and rarely, blood dyscrasias including aplastic anemia, pancytopenia, leukopenia, agranulocytosis, may occur. Appearance of L.E. cells and methaemoglobinaemia have been occasionally described.

(f) **Drug interactions :** Drug interactions with phenytoin are relatively frequent. Drugs like isoniazid, chloramphenicol, coumarin anticoagulants and sulfonamides are reported to prolong the half-life of phenytoin by inhibiting the phenytoin metabolism. Even a minor degree of such inhibition can cause disproportionate changes in serum concentrations leading to toxicity. Further, phenytoin has marked enzyme inducing properties and can stimulate the metabolism of many drugs such as contraceptive steroids, coumarin anticoagulants, glucocorticoids and vitamin D, thereby reducing their therapeutic efficacy. Dangerous hyperglycemia has been reported in diabetics receiving phenytoin. This is probably due to inhibition of insulin secretion by phenytoin.

Intravenous administration at an excessive rate

in the emergency treatment of cardiac arrhythmias or status epilepticus is known to cause cardiovascular collapse or severe C.N.S. depression.

Chronic administration of folic acid can reduce the effectiveness of phenytoin.

Preparations and dosage : Phenytoin sodium I.P. is available in tablets of 50 and 100 mg. Intravenous preparation containing 50 mg/ml. is also available. Intravenous dose should not exceed 50 mg. per minute. *It should not be given intramuscularly.*

Therapeutic uses :

(i) *Grand mal* : It is an important drug in the treatment of grand mal epilepsy. The drug abolishes grand mal seizures in nearly 60 per cent of the patients and reduces the severity and frequency of attacks in another 15 to 20 per cent.

(ii) *Psychomotor seizures* : Phenytoin is preferred to phenobarbitone in this type of epilepsy.

(iii) *Focal cortical epilepsy* : The drug often controls but does not completely abolish the seizure activity. It is also occasionally useful in hypersarrhythmia.

(iv) *Cardiac arrhythmias* : Discussed in Chapter 25.

(v) It has been used with some success in certain types of neuralgia, including trigeminal neuralgia, in diabetic neuropathy with unpleasant subjective symptoms and in chorea.

Other hydantoins : These are methoin (Mephenytoin, Mesantoin) and ethotoin (Peganone), with pharmacological properties and adverse reactions similar to those of phenytoin. They are, however, inferior to phenytoin.

II. Barbiturates :

PHENOBARBITONE : Phenobarbitone is discussed in detail elsewhere. Its sphere of antiepileptic activity is similar to that of diphenylhydantoin but in addition it raises the seizure threshold. Phenobarbitone and phenytoin are often combined in the treatment of grand mal, resistant cases of focal cortical seizures and hypersarrhythmia.

Such a combination helps to reduce the adverse effects of both drugs by keeping their individual doses below the toxic levels. The daily dose for anticonvulsant activity varies from 60 to 180 mg. given in divided doses. Larger (x2) doses for the first 3-4 days help in more rapid control of seizures but produce greater drowsiness.

The main advantages of phenobarbitone are its low cost and the rarity of systemic toxicity. Depression, drowsiness and lethargy can sometimes occur. However, drowsiness tends to disappear after a few weeks of treatment or can be effectively countered by a small dose of amphetamine. Nystagmus and ataxia are seen with larger doses. Megaloblastic anemia has also been reported.

Sudden cessation of phenobarbitone therapy after its prolonged use is dangerous as a marked increase in the frequency of convulsions and even status epilepticus are likely to occur. It must be remembered that convulsions following phenobarbitone withdrawal are difficult to control by diphenylhydantoin. Hence, while switching over from phenobarbitone to diphenylhydantoin, the dose of phenobarbitone must be reduced gradually and that of diphenylhydantoin increased slowly, till the latter drug fully takes over. Phenobarbitone is of limited value in temporal lobe epilepsy and may aggravate petit mal seizures. It may produce excitement or hyperactivity in children and in old people.

MEPHOBARBITONE (Mebaral) : Mephobarbitone is less sedative, less potent and more expensive than phenobarbitone. Its anticonvulsant effect probably depends upon its degradation to phenobarbitone in the body. Its sphere of activity is identical to that of phenobarbitone.

PRIMIDONE (Mysoline) : Primidone is a congener of phenobarbitone, and resembles phenobarbitone in many laboratory anticonvulsant effects, but is much less potent. It is useful in grand mal, psychomotor and myoclonic epilepsy. It is often combined with diphenylhydantoin.

Primidone is readily absorbed and uniformly

distributed throughout the body following oral administration. After absorption, it is converted to two active metabolites, phenobarbitone and phenylmalonamide (PEMA). The drug is mainly metabolized in the liver. Approximately 60 to 80 per cent of the ingested dose is excreted in urine within 24 hours.

Adverse effects are rare and they tend to disappear with continuation of medication. Common adverse effects include anorexia, nausea, drowsiness, malaise and headache. Sometimes, it produces a toxic syndrome characterised by acute vertigo, ataxia, diplopia and dysarthria. Skin rashes, dependent edema, personality changes and sexual impotence have also been reported. It may rarely cause megaloblastic and aplastic anemias, leukopenia and agranulocytosis.

The drug is given initially in the dose of 125 mg. daily in divided doses, increasing gradually upto 250 mg. four times a day.

III. Iminostilbenes :

CARBAMAZEPINE (Tegretol, Mazetol) is tricyclic (iminostilbene) compound with structural resemblance to the antidepressant drug imipramine.

Pharmacological actions : Carbamazepine is effective in the treatment of temporal lobe and grand mal seizures, more so in the former. Further, it is claimed to produce beneficial effect on the personality of the epileptic patient. In many instances, restlessness, irritability and psychomotor retardation improve, the patient becomes more attentive and is capable of improved concentration.

Carbamazepine is useful in the treatment of trigeminal neuralgia, a condition characterised by paroxysms of intense pain of stabbing nature within the distribution of trigeminal nerve, without sensory loss or other evidence of organic disease of the nerve. This condition, because of its paroxysmal nature, tendency to relapse and partial response to diphenylhydantoin, has been regarded as a type of epilepsy. Carbamazepine is remarkably specific for trigeminal neuralgia and

probably for the related syndrome of glossopharyngeal neuralgia. It has also been used successfully to alleviate the subjective symptoms of diabetic neuropathy. Carbamazepine has the same electrophysiological effects on heart as phenytoin.

Absorption, fate and excretion : Oral absorption is slow; overall bioavailability however, approaches 90%. It is metabolized by the liver (98%). Children metabolize the drug faster than do adults. It is a potent enzyme inducer and accelerates its own metabolism as well as that of many other lipid soluble drugs. The plasma half-life, initially 24-36 hours, falls to around 12 hours on chronic dosing because of auto induction.

Adverse reactions: Generally, these appear within the first week of treatment and include nausea, anorexia, giddiness, vomiting, ataxia, mental confusion and skin rash. Diplopia and blurred vision are not infrequent. They are commoner in elderly than in young patients and a reduction in the dose diminishes their frequency. They, however, make driving dangerous. The serious toxic effects reported include obstructive jaundice, peripheral neuritis, agranulocytosis, thrombocytopenia and aplastic anaemia. Long term use of carbamazepine may cause insidious development of sluggishness, both mental and physical. The loss of physical and mental drive can be so gradual that the patient and the family may wrongly attribute it to the normal process of ageing.

Because of enzyme induction it accelerates the metabolism of oral contraceptive pill, theophylline, corticosteroids and warfarin. On the other hand, cimetidine, diltiazem, erythromycin, isoniazid and verapamil inhibit its metabolism. It is a minor teratogen.

Preparations and dosage : It is available as 200 mg. tablets. The initial dose is 100 mg. twice a day, gradually increased to 600-1200 mg. per day in temporal lobe epilepsy and to 400-800 mg. in neuralgias.

Therapeutic uses : It is used singly or in combination with other drugs in the treatment of temporal lobe or grand mal epilepsy. In trigeminal

neuralgia, the drug usually controls the paroxysms of pain within 24 to 48 hours; in some cases, however, pain may be controlled only after several weeks of drug therapy. A complete relief of pain is obtained in approximately 50 per cent of cases, and continued treatment for 6 months satisfactorily controls 80 per cent of the cases; the maintenance dose, however, may have to be increased from time to time to prevent a recurrence. It has also been used in the treatment of diabetes insipidus of pituitary origin, because of its ADH stimulating effect. Carbamazepine is also used as an alternative to lithium carbonate (see Chapter 11) in the management of manic-depressive psychosis.

IV. Succinimides :

This group includes three drugs : ethosuximide (Zarontin), methsuximide (Celontin) and phen-suximide (Milontin). Phensuximide, the oldest among the three is the weakest and is now rarely used.

ETHOSUXIMIDE (Zarontin) : This is the most frequently used succinimide.

Pharmacological actions : It is effective only in petit mal epilepsy, in which condition it is more effective than trimethadione.

Absorption, fate and excretion : It is completely absorbed from the G.I. tract and is present in the plasma mostly in the free form. About 20% is excreted unchanged in the urine and the rest is metabolized by the liver. Its plasma half-time is 30 hours in children and 60 hours in adults.

Adverse reactions : These consist of anorexia, nausea, vomiting, drowsiness, dizziness and occasionally parkinsonism. Skin rashes and blood dyscrasias have been reported. It may rarely cause systemic lupus erythematosus, psychic disturbances and can unmask grand mal epilepsy.

Preparations and dosage : It is available as 250 mg. capsules and as a syrup (250 mg. per 5 ml.). The usual starting dose is 250 mg. per day in children. It is increased by 250 mg. increments at

weekly intervals till the seizures are controlled. A daily dose of 750-1000 mg. (generally given in a single dose) is usually not exceeded.

Therapeutic uses : It is the drug of choice in petit mal epilepsy. Concurrent administration of phenobarbitone may be needed to control associated or unmasked grand mal epilepsy.

METHSUXIMIDE (Celontin) : Its pharmacological actions, adverse effects and therapeutic uses are similar to those of ethosuximide. It is claimed not to aggravate grand mal epilepsy. Moreover, it can be used, along with other drugs, in the treatment of temporal lobe epilepsy. It is used in the dose of 500 mg. daily, given in 2-3 divided doses, increasing to 2.0 g. per day, as needed.

V. SODIUM VALPROATE (Epilim, Depakene) : Sodium valproate has a simple chemical structure, being sodium dipropyl acetate.

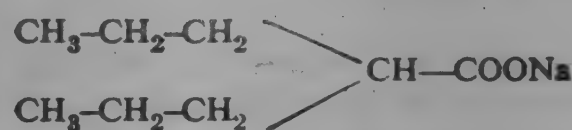


Fig. 7.2 : Sodium Valproate

Pharmacological actions : Sodium valproate is of established value in petit mal, where it is as effective as ethosuximide. However, in patients with pure petit mal, ethosuximide is considered as the drug of first choice because it is less liable to cause gastrointestinal adverse effects than sodium valproate. Further, sodium valproate is expensive at present and has been reported to produce serious hepatic damage in some patients. In patients who have both petit mal and grand mal seizures, sodium valproate may be the drug of

choice as it is able to control both types of seizures. It has also been used successfully in myoclonic seizures and with variable success in akinetic seizures and infantile spasms. It is not particularly effective in cortical focal epilepsy nor in temporal lobe epilepsy. It is claimed that it does not alter the patient's behaviour, alertness and cognitive function, that result in good learning ability and performance. Inhibition of gamma aminobutyrate transaminase has been proposed as the mechanism of the antiepileptic action of this drug. Potentiation of post-synaptic GABA activity and a decrease in brain levels of excitatory amino acids may also play a part.

Absorption, fate and excretion : Sodium valproate is rapidly and almost completely absorbed after oral administration. Eighty to 95% of plasma valproate is protein bound. More than 90% is metabolized in the liver and the plasma $t_{1/2}$ is about 15 hours in epileptic patients. The urinary ketone test may be falsely positive in patients on valproic acid.

Adverse reactions : The main adverse reactions are nausea and vomiting. It increases appetite and may cause weight gain. Dose related hair loss may occur. Hepatic damage with death has been reported during treatment with this drug. The other adverse effects are sedation, ataxia, incoordination, thrombocytopenia and pancreatitis but occur infrequently. Sodium valproate inhibits platelet aggregation, although this is unlikely to be of clinical significance unless the patient is also on other drugs that affect coagulation. It is a good precaution to do baseline hepatic function studies before starting sodium valproate.

Spina bifida has recently been associated with its use during pregnancy.

Preparations and dosage : Sodium valproate is available as capsules containing the equivalent of 250 mg of valproic acid and syrup containing the equivalent of 250 mg of valproic acid per 5 ml. Therapy is initiated with the daily dose of 15 mg/kg in divided doses in adults and in children. This may be increased by 5 to 10 mg/kg/day at weekly intervals upto 30 mg/kg/day. Doses as high as 60 mg/kg/day have been used in some patients.

Therapeutic uses : Sodium valproate is of established value in petit mal seizures. It can also be used when patient has both grand mal and petit mal epilepsy.

VI. Oxazolidinediones :

TROXIDONE (Trimethadione): Troxidone was synthesized by Spielman in 1944 and was introduced in therapy of petit mal epilepsy by Lennox in 1945.

Pharmacological actions : In human beings troxidone selectively controls petit mal epilepsy. The mechanism of this action is, however, ill-understood. The main site of action of troxidone is probably in the thalamus, where it raises the threshold of excitability of the thalamic nuclei and thus prevents the spread of electrical activity to the thalamus. Unlike phenytoin, troxidone does not affect the P.T.P. at synapses, but it offers complete protection from leptazol induced convulsions in experimental animals.

The drug is effective in majority of patients with petit mal. In patients in whom it is effective, the E.E.G. reverts completely to normal. This is in contrast to the effect of diphenylhydantoin in grand mal. Control of petit mal with trimethadione takes 3-4 days.

In patients with grand mal attacks, it may aggravate the condition. Hence, in patients with both petit mal and grand mal epilepsies, troxidone must be combined with phenobarbitone.

Absorption, fate and excretion : The drug is well absorbed from the gastrointestinal tract and is metabolized in the liver. It is possible that one of its degradation products (D.M.O. or 5, 5-dimethyl-2, 4-oxazolidinedione) contributes to its antiepileptic activity.

Adverse reactions : The most frequent adverse effects are drowsiness and hemeralopia (blurring of vision in bright light). The former can be controlled by amphetamine. The latter, probably a sensitivity reaction, occurs in 30 per cent of the adult patients and is rare in children. It can be relieved by wearing dark glasses. Nausea and hiccough are fairly frequent.

More serious but rare toxic effects are morbil-

iform skin rashes, exfoliative dermatitis, blood dyscrasia, nephrosis and hepatitis. The interval between the initial administration of the drug and the appearance of clinical renal disease ranges from 4 months upto 2 years. Other toxic manifestations include behavioural and personality changes, precipitation of systemic lupus erythematosus and polyarthropathy. Trimethadione is teratogenic and should not be used in women of the child bearing age.

Troxidone I.P. is available as 300 mg. capsules.

Uses : It is used in patients with petit mal who are inadequately controlled by or who do not tolerate other drugs.

PARAMETHADIONE (Paradione) : This is a chemical congener of trimethadione with similar therapeutic uses, dosage and toxicity. The drug is used in petit mal seizures refractory to ethosuximide.

VII. Benzodiazepines :

CLONAZEPAM : This drug is useful in the

treatment of petit mal, myoclonic seizures and infantile spasms. In petit mal, it is used in patients who do not respond to ethosuximide and sodium valproate and not as the primary drug. Tolerance develops and breakthrough seizures may occur after 1 to 2 months of therapy. It has also been used as an adjunct to phenobarbitone and phenytoin in the treatment of grand mal.

Clonazepam and diazepam are believed to act by increasing the effectiveness of the inhibitory neurotransmitter, G.A.B.A., within the CNS.

The serious adverse effects are mainly neurological and comprise drowsiness, ataxia, personality changes, slurred speech, tremor, vertigo and confusion. These are dose-related. Skin eruption, anemia, leucopenia and thrombocytopenia have been reported. It is liable to cause respiratory depression and to increase the salivary and bronchial secretions. The other adverse effects involve the cardiovascular, the gastrointestinal and the genitourinary systems. Tolerance is known to occur during chronic administration, and psychic and physical dependence have been reported to occur.

Table 7.1: Drugs commonly employed in the treatment of epilepsy

Drug	Steady State (days)	Serum Half-Life Hours		Dose * mgs/day	Dose Interval	Therapeutic serum concentration (mcg/ml)
		Adults	Children			
Phenytoin sodium	variable 7-8	24	20	100-400	od	10-20
Phenobarbitone	>21	120-140	72-96	60-180	od	15-25
Primidone	4-7	15	8	500-1500	od	5-12
Carbamazepine	3-4	12	8	200-1500	bd, tds	4-12
Ethosuximide	7-10	55	30	500-2000	bd, tds	40-100
Valproate	1-4	15	11	500-2000	bd, tds	50-100

od = once daily
bd = twice daily
tds = thrice daily.

* In adults

Therapy is initiated in adults and in children over 10 years of age with oral administration of 0.5 mg three times a day; the dose is gradually increased to maximum of 20 mg per day. Smaller doses are used in younger children.

DIAZEPAM : When given intravenously, diazepam can be life saving in status epilepticus and is the treatment of choice in this condition as well as in convulsions of non-epileptic origin. Its chronic use in epileptic disorders is not practicable because of the development of tolerance.

For pharmacology of benzodiazepines see Chapter 11.

VIII. Miscellaneous :

BROMIDES : The bromides are effective mainly in grand mal seizures and their full effect develops only 2 to 3 weeks after institution of therapy. They produce cumulative toxicity characterised by drowsiness, skin rashes and psychotic and neurological disturbances, collectively termed bromism. They are now rarely employed in therapy. For details, see the earlier editions of the book

ACETAZOLAMIDE (Diamox) : The antiepileptic activity of this drug is correlated with its carbonic anhydrase inhibitory activity within the central nervous system. As an adjunct, it is occasionally effective in petit mal cases and in patients with grand mal who show increased frequency of seizures during menstruation (See Chapter 35).

SULTHIAME (Ospolot) : Sulthiame is a sulfonamide derivative. It is satisfactorily absorbed from the gastrointestinal tract and more than 80 per cent of the drug is excreted by kidneys. It has been claimed to be effective in temporal lobe epilepsy, and to a lesser degree in grand mal and 'myoclonic' seizures. It has been used in the dose of 100-600 mg/day as an adjunct to other antiepileptic drugs.

Adverse reactions : These include nausea, anorexia, weight loss, apathy, ataxia, blurring of vision, photophobia, psychotic reactions, paraes-

thesias, kidney damage and crystalluria. The drug may precipitate status epilepticus. Tachypnoea, which occurs in as many as 30 per cent of patients, is a primary effect of the drug and not secondary to drug-induced metabolic changes.

PHENACEMIDE or phenylacetylurea is a straight chain chemical analogue of 5 phenylhydantoin (Fig. 7.1).

It is well absorbed from the gastrointestinal tract and is completely metabolized by the liver. The action of a single dose persists for 4 to 5 hours. It is a 'wide spectrum' antiepileptic drug, being effective in grand mal, psychomotor and petit mal seizures. Unfortunately, the incidence of adverse reactions is high. It causes mental changes, ataxia, gastrointestinal symptoms, skin rashes, blood dyscrasias, hepatitis with jaundice and nephritis. It may induce paranoid schizophrenic episodes in patients with psychomotor epilepsy.

Uses : Its high toxicity has restricted the use of phenacemide to only psychomotor epilepsy refractory to other drugs. It may be used in combination with phenobarbitone or diphenylhydantoin.

PHENETURIDE, a new derivative, is less toxic and is given in the dose of 200-1000 mg. daily. It has now replaced phenacemide in therapy.

AMPHETAMINE is a useful adjuvant in the treatment of grand mal and petit mal seizures. In the former, it is especially useful in countering the drowsiness caused by phenobarbitone. Paradoxically, it often improves and sedates mentally retarded children with hyperkinetic epilepsy which is generally aggravated by phenobarbitone.

Aims and principles of treatment of epilepsy : The aim of drug therapy should be to achieve complete control of seizures with minimum of drugs and an absence of adverse effects. In practice, this is not always possible. Antiepileptic drugs must be continued even if they abolish the seizures only partly as it has been

shown that a series of major seizures damages the brain.

Surgical treatment can cure a few cases. In the absence of life threatening intracranial space occupying lesions, it is indicated only when attacks become intractable and are inadequately controlled by drugs. Surgery, however, must be followed by life long drug therapy because of the secondary abnormal foci it creates.

Social and genetic aspect : Epilepsy should be considered as an illness and not a social stigma. As long as an epileptic is willing to be careful and to take the treatment continuously under proper supervision, he should be given a fair chance in finding a job for himself. Occupations involving driving of vehicles and working with machines near water or at heights are not suitable for epileptics. Likewise, swimming is a forbidden sport. Within these limits, a well controlled epileptic may be a good employee if he knows his limitations.

Marriage may be permitted provided the other partner is not an epileptic and has a normal E.E.G.

Use of antiepileptic drugs : Most of the drugs available are effective and reasonably safe.

An ideal antiepileptic drug should

(a) be effective in all varieties of epilepsy and should preferably have a direct action on the epileptogenic focus;

(b) be quick acting with a long duration of action (24 hours or more);

(c) possess minimal side effects and be non-toxic and nonaddicting; and

(d) be orally effective and cheap.

Although an ideal drug is not available, the currently available drugs, used judiciously and continuously, abolish seizures completely in 60-80 per cent of the patients and reduce their frequency in another 10-20 per cent. This is usually achieved without producing intolerable adverse effects. Patients can be restored to a full working life, making social rehabilitation possible. Occasionally, these drugs will suppress the abnormal

electrical activity and after therapy for years, may produce complete clinical cure. This is especially true in patients with petit mal epilepsy.

To achieve best results with drugs, the following must be carefully observed:

(i) Proper initial evaluation of the case is necessary for selecting the most suitable drug in a given case. It must be remembered that the choice of the drug depends upon the site of the epileptogenic focus and hence on the type of epileptic seizure, and not on whether it is idiopathic or symptomatic.

(ii) The drug therapy should be simple. Treatment should be started with the least toxic and the most established primary antiepileptic drug appropriate for the particular seizure. Changes in therapy should be made after careful weighing of pros and cons and not every time a new drug appears on the market.

(iii) Therapy should be started with a single drug in small dose, increasing it gradually till the maximum benefit without a corresponding increase in toxic effects is obtained. Repeated E.E.G. evaluation and determination of the plasma level of the drug may help in difficult cases. A close watch should be kept for adverse systemic and neurological effects of the drug used.

(iv) When adequate control is not achieved by a single drug, a second drug (preferably from a different chemical class) is added to the regimen. When a drug combination is used, each drug should be prescribed separately and fixed-dose drug combinations should be avoided. The patient, or in case of children, the parents, should be educated to observe proper precautions, to keep a seizure record and to attend the follow-up clinic regularly.

(v) It has been customary to prescribe the antiepileptic drugs 2-3 times a day. Patients often tend to forget one or more of the doses. As control of seizures depends upon sustained therapeutic plasma levels of the drug round the clock, such non-compliance tends to lead to poor seizure control. With phenobarbitone, phenytoin, primi-

done and ethosuximide, pharmacokinetic studies have now established that sustained therapeutic plasma levels can be achieved by giving the entire daily dose just once a day. Further, this is likely to elicit better patient-compliance and to ensure better seizure control. Sodium valproate is best prescribed on a twice a day basis and carbamazepine on a twice (occasionally thrice) a day basis.

(vi) When experience shows that in a given patient the frequency or likelihood of attacks is increased under certain stressful circumstances e.g. examination or social events, it is advisable to increase the dose, often to the limit of tolerance, well in advance of the event, and to reduce it gradually afterwards. Trauma, including that of surgery, also increases the drug requirement.

(vii) Adequate trial (for 2-3 months) should be given to an antiepileptic drug before rejecting it in favour of another one. While changing from one drug to another, the changeover must be gradual. The first drug must be tapered off slowly while the second one is introduced in gradually increasing doses. This is done to prevent precipitation of status epilepticus following sudden cessation of one drug.

(viii) Epileptic seizures that initially responded to drug therapy sometimes escape from control. In the case of phenobarbitone, primidone, phenytoin and carbamazepine, the escape may be due to induction of drug-metabolising, hepatic enzymes.

(ix) In patients who have had a single major fit the treatment may be stopped after a few weeks. Most patients who have had two or more attacks will need treatment for their lifetime. However, an attempt may be made to discontinue the antiepileptic therapy in those individuals with idiopathic grand mal epilepsy who have remained seizure free for 3-4 years while on drugs. Patients with focal seizures are more likely than those with grand mal seizures to have a recurrence of seizures. The drug should be tapered off slowly over weeks or months before stopping it. It is important that the physician should have an optimistic and cheerful attitude towards the patient's problems and should stress the bright rather than the

gloomy side of drug therapy.

(x) It is important to remember that certain drugs should be avoided in epileptic patients, as they are capable of precipitating fits in such cases. The group includes phenothiazines, tricyclic antidepressants and many antihistaminics. Of course, an epileptic should not be given analeptic drugs.

(xi) The risk of congenital malformations and of mental retardation in infants exposed in utero to anticonvulsants appears to be 2-3 times that in the general population. It would appear to be much higher with the trimethadione than with phenobarbitone and phenytoin. However, it must be pointed out that 90% epileptic mothers treated with antiepileptic drugs will bear normal children. Further, sudden cessation of antiepileptic drug is liable to precipitate status epilepticus and consequently abortion. Hence, antiepileptic drugs should not be abruptly stopped during pregnancy. Their dose should be reduced to a minimum especially during the first trimester. Medical termination of pregnancy should be seriously considered in a woman who is on trimethadione. Women on phenobarbitone, phenytoin or primidone should receive folic acid supplements during pregnancy. The newborn of mothers who have received phenobarbitone, primidone or phenytoin should receive vitamin K soon after birth, in order to prevent bleeding due to deficiency of vitamin K dependent clotting factors. The newborn of mothers who have received any antiepileptic drug during pregnancy should be examined carefully for congenital abnormalities.

TREATMENT OF VARIOUS TYPES OF EPILEPSY

Drugs used in the treatment of epilepsy may be clinically classified into :

(A) *Those that are effective in petit mal* : ethosuximide, troxidone, amphetamine, sodium valproate, diazepam and acetazolamide; and

(B) *Those that are effective in all other varieties* : phenobarbitone, diphenylhydantoin, primidone, sulthiam, pheneturide, carbamazepine and diazepam.

I. GRAND MAL :

(a) **During an epileptic attack :** If a known epileptic person is under close observation, it may be possible to recognize an attack early enough to avert a fall. More often, by the time a fit is noticed tonic or clonic phase has already started.

When flaccidity of the muscle supervenes after the clonic phase is over, the patient can be choked by his own saliva and by his tongue falling back into the pharynx. This can be prevented by turning the patient into a semiprone position and if available, by inserting a pharyngeal airway. The patient should then be watched till he recovers consciousness. A child, unless it is known to be an epileptic, should be admitted to a hospital at this stage, as meningitis is a common cause of convulsions in childhood. In adults, the need for hospitalization is less urgent.

(b) **Prevention of attack :** An epileptic should be advised to use hard pillow to prevent being smothered, if an attack occurs during sleep.

Phenobarbitone should be started in the dose of 30 mg. twice or thrice a day and the dose should be increased gradually, until seizures are controlled or a total daily dose of 200 mg. is reached. Drowsiness from phenobarbitone can be countered by a small dose of amphetamine (2.5 mg. once a day). If seizures continue at this dosage level, add phenytoin sodium.

When phenytoin is used in the maintenance dose (300-400 mg/day) from the outset, therapeutically effective plasma levels are achieved only after 7-10 days. When the need to control seizures is more urgent, therapeutic plasma levels can be reached within 12-24 hours by giving a loading dose of 1 g. before commencing the daily maintenance dosage schedule. The maximum tolerated maintenance dose of this drug for an adult is 600 mg. per day.

There is considerable variation in the bio-availability of phenytoin sodium from the many marketed preparations. This might account for the sudden appearance of toxicity or of loss of seizure control on changing the proprietary preparation of phenytoin without changing its dose.

Primidone alone or in combination with phenytoin is a useful alternative if phenobarbitone phenytoin combination fails to control the seizures. The change over, if required, must be very gradual. Carbamazepine is also useful in such cases. Adjuvant drugs such as sulthiam may be added to phenobarbitone and diphenylhydantoin in refractory cases.

Once seizures are under control, the drug or drug combination must be continued for a least 2 to 3 years after the last seizure episode.

When a patient is being maintained on an effective drug combination, the dose should be raised prophylactically for a few days before circumstances and events known to precipitate seizures. Patients must be warned against sudden cessation of drug treatment. Drug treatment is not effective in preventing mental deterioration. This is, however, rare in well controlled epileptics.

Epilepsy during drowsiness is a condition where fits occur when the patient is drowsy but not asleep. Anticonvulsants like phenobarbitone which produce drowsiness increase the frequency of attacks in this condition and must be avoided.

Phenobarbitone is the drug of choice for grand mal epilepsy in children under the age of 5 years, as they do not seem to tolerate phenytoin as well as older children and adults do.

II. CORTICAL, FOCAL AND MINOR EPILEPSY:

The drug treatment of these conditions is similar to that of grand mal epilepsy.

III. TEMPORAL LOBE EPILEPSY:

This is often refractory to drug therapy. Phenobarbitone is rarely effective. Phenytoin, carbamazepine and primidone are the preferred drugs in this condition.

IV. PETIT MAL:

In patients suspected of having petit mal epilepsy, it is essential to confirm the diagnosis by an E.E.G. as the specific drugs are effective only in patients with typical E.E.G. changes. It is also essential to inquire about concomitant grand mal attacks as anti-petit mal drugs

are liable to aggravate grand mal.

Ethosuximide is the drug of choice in this condition. It is given in the dose of 250 mg. three times a day, increasing the dose upto 1500 mg. per day, if necessary. If the patient cannot tolerate ethosuximide or it fails to control the seizures, either sodium valproate or clonazepam may be used.

Amphetamine (2.5 to 5 mg. twice a day) and acetazolamide (250 mg. thrice daily) are useful adjuncts but by themselves are not much effective.

If the patient gets grand mal attacks as well, phenobarbitone or diphenylhydantoin must be given in addition to ethosuximide. Alternately sodium valproate may be used as a single drug.

As drugs effective in controlling petit mal can aggravate even latent grand mal epilepsy and as petit mal is sometimes followed by grand mal later in life, some workers feel that all patients with petit mal should be prescribed phenobarbitone in addition to ethosuximide whether or not they have grand mal epilepsy.

Drug treatment of petit mal can be withdrawn 3-4 months after cessation of attacks. It is rare for this variety of epilepsy to recur after stopping the therapy.

V. MYOCLONIC SEIZURES: These are often refractory to treatment. Sodium valproate seems to be the drug of choice, followed by clonazepam.

VI. INFANTILE SPASMS are best treated with ACTH or corticosteroids.

VII. POST-TRAUMATIC EPILEPSY: Head injury predisposes to the development of epilepsy. There is some clinical evidence that prophylactic treatment with phenobarbitone or/and phenytoin may prevent this.

VIII. FEBRILE CONVULSIONS: Because it takes time to reach therapeutic plasma levels, phenobarbitone, started during individual febrile episodes, may be ineffective in preventing febrile

convulsions. Hence, in infants and children who have shown high susceptibility to febrile convulsions, chronic prophylactic therapy with phenobarbitone may have to be initiated. Further, such chronic prophylactic therapy should be started in a child with a febrile convulsion (a) if the convulsion was focal or prolonged (longer than 15 minutes); (b) if the patient has any neurological abnormality; or (c) if any sib or either parent of the patient has epilepsy. The child should be treated for 2 years or for 1 year after the last seizure, whichever is longer. During an attack of a febrile convulsion, rectal administration of diazepam in the dose of 500 µg/kg is rapidly effective.

IX. STATUS EPILEPTICUS: This term is used to indicate repeated grand mal seizures without recovery of consciousness between the attacks. It is a medical emergency and such patients must be hospitalized for proper intensive care treatment. The patient should first be given 50 ml of 50% glucose intravenously. The administration of other drugs intravenously needs the availability of cardio-respiratory resuscitative support. Diazepam given intravenously is the treatment of choice for controlling the seizures. It may be given in the dose of 10 mg., I. V., slowly (over 5 minutes) in adults, 5 mg. for children over 7 years of age and 2.5 mg. for those between 1-7 years of age. The dose may be repeated twice more at 15 minute intervals. The dose may be repeated in 2 to 4 hours, if necessary. Hypotension and respiratory depression should be watched for, especially in patients who have received barbiturates earlier. Cardiac arrest has also been reported after I. V. diazepam. If I.V. administration is not possible, diazepam may be administered rectally: 10 mg in adults and children over 3 years, and 5 mg in children 1-3 years and in elderly patients; it may be repeated, if necessary, after 5 minutes. Phenobarbitone sodium (10-20 mg/kg) at the rate of 60 mg./min. I.V. is also effective but takes a longer time to act. Phenytoin, to be effective during an emergency, must be given in doses of 0.5 to 1.0 g. I.V. at the rate of 50 mg./min; it is very irritant and

occasionally causes sudden death.

Inhalation of volatile general anaesthetics like ether and intravenous thiopentone sodium are other methods for controlling convulsions in resistant cases. As a last resort, lidocaine may be given by intravenous infusion in the dose of 1-3 mg/minute. However, it must be remembered that an overdose of lidocaine itself can cause convulsions.

Patients in status epilepticus are liable to develop hyperpyrexia. It should be looked for and treated immediately.

Between convulsions, a soft object, large enough not to be swallowed, such as a folded napkin, should be inserted between jaws to prevent tongue biting during subsequent convulsions.

Once the seizures are controlled, parenteral loading dose of phenobarbitone or phenytoin should be given; further management is that of an unconscious patient for the next 24 to 48 hours,

with attention to maintenance of airway, hydration, nutrition, bladder function and prevention of chest infection.

Immediately on recovery of swallowing, the patient should be put on the grand mal antiepileptic drug therapy; he should be advised to attend epilepsy clinic regularly on discharge from the hospital.

Emergency management of convulsions due to other disorders such as febrile convulsions, withdrawal of sedatives (including barbiturates), tetanus, eclampsia, cerebral hemorrhage, poisoning from convulsive agents and during administration of local anaesthetics is similar to that of status epilepticus. Parenteral diazepam is the drug of choice. Parenteral phenytoin is not useful in these conditions. The same is true of convulsions occurring during the withdrawal of C.N.S. depressant agents in addicts.

8 Opioid Analgesics

Pain is an unpleasant sensation which only the individual himself can appreciate; it cannot be objectively defined satisfactorily. There is no doubt that pain acts as a warning signal against disturbances either in the body or in the external environment of an individual and thus has a protective function. However, on many occasions pain seems pointless, only contributing to the discomfort of the subject. As a symptom, pain demands instant relief and in practice dramatic relief of pain by drugs highly impresses a layman.

Pain receptor organs are distributed throughout the body. Clinically, pain can be considered as:

- (a) Superficial or cutaneous pain.
- (b) Deep non-visceral pain from muscles, joints, ligaments and bones,
- (c) Visceral pain,
- (d) Referred pain and
- (e) Psychogenic or functional pain.

Pain arising from the skin and from the deep structures like muscles, bones and joints is also termed as *somatic pain*. Somatic pain is usually well defined and is generally caused by inflammatory reaction in the tissues; it may be accompanied by contraction of the surrounding skeletal muscles as in patients with rheumatoid arthritis or gout. However, other causes such as direct irritation of a nerve as in trigeminal neuralgia, herpes zoster, increased pulsation of the intracranial arteries as in migraine, or vascular insufficiency as in thromboangitis obliterans are also incriminated in the genesis of somatic pain.

Pain arising from the skin and superficial mucous membrane or nerves is felt as pricking, if brief, and stinging, smarting or burning if prolonged. The sensation of 'pinprick' elicits a withdrawal reaction of a part or all of the organism.

Such a reflex is protective in nature.

Deep nonvisceral pain usually has a dull character and it may be accompanied by a sickening sensation due to an autonomic response. Sometimes, it tends to spread to other areas and may even occur as referred pain. Blood pressure and pulse, however, are not much affected.

Visceral pain, unlike the somatic pain, is diffuse, less easily localised and often 'referred'. It is dull-aching in character and is often accompanied by sweating, nausea, fall in blood pressure and even shock. In addition, muscle rigidity and hyperaesthesia are common accompaniments. In practice, visceral pain may be due to spasm (renal or biliary colic), ischemia (myocardial infarction), inflammation (appendicitis, pancreatitis) or stimulation of the sensory nerve endings (peptic ulcer).

Deep pain, whether visceral or somatic in origin, may sometimes be misinterpreted as if it is coming from some part of the body other than the actual site of stimulation. This is called *referred pain*. Thus, cardiac pain is commonly referred to the left arm and diaphragmatic pain to the shoulder. Usually, the pain is referred to a cutaneous area which receives its nerve supply from the same spinal segment as the affected viscus and this phenomenon is probably due to convergence of several cutaneous and visceral afferent fibres on the same secondary neurones at some point in the pain pathway.

Although various theories have been proposed to explain the pain mechanism none can explain all its aspects. The assimilation of sensory pain at the level of consciousness depends on various factors such as the nature of sensory receptors, the intensity of the impulses transmitted to the central nervous system, their integration and finally their

modulation by other sensory information. The conscious appreciation of pain appears to depend upon the widespread activity of the entire cortex and individuals differ widely in their reactions to similar painful experiences.

Psychogenic or functional pain is usually a vague pain which follows no definite anatomical pattern of distribution. Such pain is usually continuous from day to day and involves more than one part of the body. It, however, does not disturb sleep. Psychogenic pain is often preceded by a phase of exhaustion while organic pain brings about exhaustion.

Pain pathway: It appears that peripheral sensation is transmitted by large diameter (L), fast conducting nerve fibres and via small diameter (S), slow conducting nerve fibres. Minimal stimulus such as touch activates the L nerve fibres. Such an impulse, on reaching the spinal cord, activates the first transmission cell and also the collateral cells in the substantia gelatinosa (SG). Anatomically, these nerve fibres are carried in the dorsal nerve roots and end in the SG at the apex of the dorsal gray horn and in the intermediate gray matter in the spinal cord. The SG cells inhibit the passage of signals and thus decrease the output reaching the higher centres. If, however, the peripheral stimulus is more intense, then both L and S nerve fibres are activated, resulting in higher output from transmission cells reaching the higher centres, leading to perception of pain. Thus, this *gate control* allows the sensory input to be decreased or augmented depending on the relative activity of L fibres and S fibres which in turn depends upon the intensity of peripheral stimulus.

The secondary axons which arise from the dorsal horn cross over to the other side around the central canal of the spinal cord and form the spinothalamic tract. The intermediate gray matter gives origin to the spinoreticular fibres which intermingle with the spinothalamic tract. In the brainstem, the spinothalamic pathway retains a lateral position and finally terminates in the thalamus and the post central gyrus and is mainly

responsible for localisation of pain sensation. The other intermingled fibres which form an ascending multisynaptic pathway terminate in the thalamus and from there to frontal and limbic systems. This system is concerned with the emotional concomitants of pain.

It appears that higher centres, through their both central inhibitory and facilitatory mechanisms, exert modulating influence on the gate mechanism. Thus, clinically the sensation of pain has several components including the emotional reaction. Painful stimuli may primarily be physical stimuli such as pressure or heat, or they may be chemical stimuli from the products of inflammation.

A variety of naturally occurring compounds are capable of eliciting pain response in experimental animals, e.g. histamine, acetylcholine, bradykinin and 5-hydroxytryptamine. One or more of these substances are also present in various venoms. However, whether endogenous release of these substances is involved in the production of pathological pain is uncertain.

The relative importance of the thalamus and the cortex in the perception of pain is still disputed. Thalamic sensation is crude and poorly localised and sensory cortex is essential for localizing and detecting variations in the intensity of pain.

Analgesics are drugs which relieve pain without causing loss of consciousness.

Experimental evaluation of analgesics: Analgesics can be evaluated in three different ways:

- (a) Prevention or relief of artificially induced pain in experimental animals.
- (b) Relief of experimental pain in human volunteers and
- (c) Relief of pathological or incisional pain in patients.

The laboratory evaluation of analgesics was formerly confined to studies on experimental pain in animals like rat, mice and guinea pigs. Pain can be evoked in these animals by intraperitoneal administration of chemical such as bradykinin,

phenylbenzoquinone and acetic acid. Alternatively, methods such as the application of a clip or radiant heat to the rat tail, placing mice on a hot plate, electrical stimulation of the incisor tooth pulp or rectal mucosa of the guinea pig or application of radiant heat to the guinea pig back, have also been extensively employed. Although highly predictive of clinical analgesic activity, these methods are still relatively crude. Further, they fail to distinguish between addicting and non-addicting analgesics. Lastly, the phenomenon of pain is highly subjective. Hence, human volunteers and non human primates are now increasingly employed for the evaluation of analgesic activity.

Monkeys can be trained to press a lever to step down the intensity of a constantly and regularly increasing shock, which they can then maintain at a relatively constant level. This level is raised by opioid analgesics. In human beings, the analgesics are evaluated either against experimentally induced pain (radiant heat, ischemia induced with sphygmomanometer cuff, intraperitoneal bradykinin) or against 'endogenous' pain (post-puerperal pain, post operative pain and pain due to malignancy). For obvious reasons, evaluation of analgesics against pathological pain is preferred to that against experimentally induced pain. It is usually desirable to compare the effects of several doses of several drugs in the same patient, before drawing conclusions.

Because of the subjective component of pain, use of a cross over double blind technic using a placebo or a standard drug is essential in evaluating various analgesic drugs in man.

Classification : Analgesics are classified into opioid and non-opioid.

I. Opioid analgesics : The word 'opiates' refers to the products obtained from the opium poppy. The term 'opioid' is used to denote all naturally occurring, semi-synthetic and synthetic drugs (not necessarily related chemically to morphine e.g. pethidine) which have a morphine like action viz relief from pain and depression of the CNS, both of which are reversed by naloxone.

These drugs were formerly called 'narcotic' analgesics because some of them (such as morphine) induce sleep. The word narcotic is derived from the Greek prefix 'narco' which means to deaden, numb. The term 'narcotic' is no longer applied to the family of opioids but is restricted in the legal sense to drugs that are capable of producing dependance.

The opioids are further classified into (a) *Agonists* which resemble morphine in most of their actions e.g. opium alkaloids and derivatives; synthetic compounds such as pethidine, methadone and propoxyphene.

(b) *Antagonists* which, by themselves, produce few effects unless an opioid agonist has been administered previously e.g. naloxone. However, when endogenous opioids are activated as in shock or stress, an opioid antagonist does produce visible effects.

(c) *Mixed agonist-antagonists* which act as agonists at one type of opioid receptors and as competitive antagonists at another type of receptors e.g. butorphanol, nalbuphine, pentazocine and buprenorphine. Patients who have received repeated doses of a morphine like drug to the point of physical dependence may experience an opioid withdrawal reaction when given a mixed agonist-antagonist.

The opioid drugs are believed to produce their effects by combining with opioid receptors which are widely distributed in the CNS and other tissues. On the basis of pharmacological data, the opioid receptors have been classified into *mu*, *delta*, *kappa*, and *epsilon* types. The vast majority of opioid drugs in current use as analgesic agents (morphine, pethidine, fentanyl, methadone) are agonists at *mu* receptors. Each may be substituted for morphine in dependant subjects. The opioid antagonists, naloxone and naltroxone, show a high selectivity for *mu* receptors but a lower selectivity for *delta* and *kappa* receptors.

Peptides with strong opiate-like analgesic and receptor binding activity are now known to be present in the CNS and other tissues. In the CNS, they are believed to act as endogenous analgesics,

as neuro-transmitters and as behaviour modulators. Beta-endorphine, a potent analgesic, is derived in the pituitary from a larger, present molecule, pro-opio-melanocortin (POMC). It is released along with ACTH and is believed to be a pain modulator in the CNS. Enkephalins, derived from pro-enkephalin, are more widespread; they are found in the pituitary, brain, G.I. tract, spinal cord, pancreas and adrenal cortex. Finally, beta-dynorphin, a derivative of pro-dynorphin, has been found to be widely distributed in the CNS. Although these peptides have affinity for more than one receptors type, Beta-endorphine has high affinity for mu-receptors, enkephalins for delta-receptors and dynorphine for K receptors. Attempts are being made to develop synthetic opioid peptides for clinical use as analgesics.

Milk and milk products contain opioid peptides such as beta-casomorphins, which are released from casin in the intestine during digestion of milk. They may modulate G.I. function on local release.

II. Non-opioid analgesics which do not interact with opioid receptors and relieve pain without depression of the CNS e.g. salicylates and related compounds.

OPIUM ALKALOIDS

Opium is the milky exudate obtained by incising the unripe seed capsule of the poppy plant *Papaver somniferum*. The poppy seeds, however, are devoid of pharmacological activity. On drying in the air, the exudate forms a gummy, brownish mass. The pharmacologically active alkaloids of opium can be divided chemically into two groups: (1) the phenanthrene group and (2) the benzyl isoquinoline group. The alkaloids constitute approximately 25 per cent of opium by dry weight. The important opium alkaloids are listed in Table 8.1.

The benzyl isoquinoline alkaloids are devoid of analgesic activity but act as smooth muscle relaxants. They are discussed in detail elsewhere.

Table 8.1 Opium alkaloids

	Name	Percentage
Phenanthrene series	Morphine	9 to 14
	Codeine	0.5 to 2
	Thebaine	0.2 to 1
Benzyl isoquinoline series	Papaverine	0.8 to 1
	Noscapine	3 to 10
	Narcine	0.2 to 0.4

MORPHINE is the most important alkaloid of opium and is used as sulfate or hydrochloride. The former occurs as fine, white, odourless crystals while the latter is obtained as crystalline powder or flakes; both salts are soluble in water.

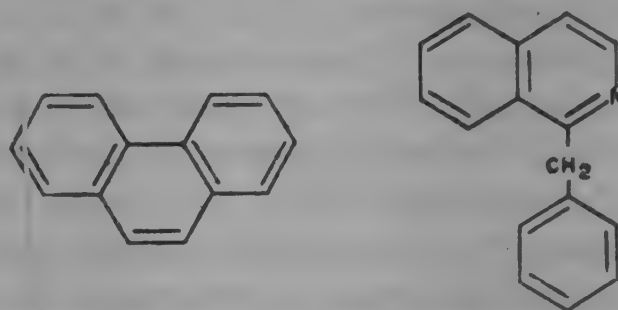


Fig. 8.1 Phenanthrene Benzyloisoquinoline

Pharmacological actions :

Central nervous system :

(a) **Analgesia** : Morphine produces relief of pain in a dose that usually does not alter the other functions of the central nervous system significantly. Thus, analgesia produced by morphine is not accompanied by slurred speech or motor incoordination as seen with general anaesthetics or alcohol. Further, other modalities such as touch, vibration and hearing are not obtunded. In subanaesthetic doses, morphine and its analogues have little effect on pinprick sensation and the withdrawal reflex, though pain arising from the tissues is well suppressed. In moderate doses, morphine is effective in relieving continuous, dull pain. Sharp, intermittent pain, caused by trauma and by visceral pathology may require larger doses for relief.

Morphine raises the pain threshold, thereby reducing the perception of pain. This action may be assisted by the feeling of well-being (euphoria) produced by morphine. This is achieved by its action probably at several sites within the CNS.

Morphine modifies the emotional reaction to pain. Thus, morphine may not completely abolish pain perception in therapeutic doses but the patients frequently regard it with detachment and it is no longer a source of concern.

Morphine also induces sleep, which itself can raise the pain threshold.

(b) *Euphoria, sedation and hypnosis*: With therapeutic doses, morphine produces a sense of emotional well-being or contentment termed euphoria. Euphoria eliminates the normal fear, panic, withdrawal and flight response to pain and aids the analgesic action of morphine. The ability to produce euphoria even in the absence of pain makes morphine one of the worst drugs of addiction. Rarely morphine may produce a sense of anxiety or fear termed *dysphoria* particularly in pain-free individuals. Sedation induced by morphine is characterized by drowsiness, decreased physical activity, difficulty in concentration and mental apathy. Thoughts and ideas may lack a logical sequence and imagination becomes extravagant, producing vivid and colourful daydreams. The inability to concentrate makes serious and purposeful intellectual effort impossible. Recently acquired functions involving skill are abolished by morphine and if the environment is favourable, sleep may be induced. In man, a single therapeutic dose of morphine produces E.E.G. changes similar to those observed during natural sleep. The psychological effects of morphine persist for a long time after its analgesic action is over. Morphine, unlike barbiturates, does not possess a significant anticonvulsant action. With an increase in the dose, deep sleep ensues and other effects like respiratory depression and vomiting appear.

The exact mechanism of morphine induced analgesia and euphoria is not known. It causes analgesia probably by selectively acting on recep-

tors situated both in the higher centers and the spinal cord. The periaqueductal gray matter of the brain stem and the thalamus has a high opiate receptor density. Within the spinal cord, opiate receptors are localized in the substantia gelatinosa, which is the first site in the CNS for the integration of sensory information. Opiate receptors are also found in the area postrema which contain the CTZ and the solitary nuclei which receive visceral sensory fibres from the vagus and the glossopharyngeal cranial nerves. This can explain the induction of nausea and vomiting and depression of the cough reflex following morphine. Opiate receptors have also been identified in the amygdala and it is possible that they are associated with influences of opiates on emotional reaction. Opioids and endogenous opioid like peptides have been shown to modify the release of acetylcholine, noradrenaline, dopamine and substance P.

In certain animals such as cats, cows, lions, bears and horses, morphine produces stimulation of the central nervous system resulting in gross restlessness and hyperthermia.

(c) *Respiration*: Morphine produces a depression of respiration partly (i) by direct depressant action on the brain stem respiratory centre and partly (ii) by reducing the sensitivity of the medullary respiratory centre to increased plasma CO₂ concentration. Retention of CO₂ brought about by initial respiratory depression by morphine increases the rate and depth of respiration to the pre-drug value. At a later stage, the hypoxic drive tends to maintain the minute volume despite diminished sensitivity of the respiratory centre to accumulated CO₂. The respiratory rate and minute volume, therefore, are not adequate monitors of respiratory depression caused by morphine. Bronchoconstriction as a result of histamine released by morphine and indifference to respiration as a result of psychological action of morphine, further enhance respiratory difficulties.

With toxic doses of morphine, breathing is entirely maintained by the 'hypoxic drive' mediated through the carotid and the aortic body

chemoreceptors and this may result in Cheyne-Stokes respiration. Inhalation of pure oxygen at this stage abolishes the hypoxic drive and produces apnoea. Hence, in such cases controlled assisted ventilation and moderate concentrations of oxygen are indicated.

(d) *Pupils* : Morphine produces miosis resulting in characteristic pin-point pupils. Miosis is countered by cholinergic blocking agents. Topical application of morphine fails to evoke miosis. The exact mechanism of action is not well defined, but it is believed to be primarily due to an action on the Edinger-Westphal nucleus of the oculomotor nerve. Pin-point pupils are characteristic of acute morphine poisoning. Morphine causes pupillary dilatation in cats whereas in birds the pupils are not affected.

(e) *Nausea and emesis* : Morphine produces vomiting by stimulation of the chemoreceptor trigger zone (CTZ) in the area postrema of the medulla. Morphine induced vomiting is abolished by nalorphine and some phenothiazines but not by antihistaminics.

In large doses, morphine depresses the vomiting centre. Thus in case of morphine poisoning, vomiting is absent and emetics are ineffective.

(f) *Cough* : Morphine depresses the cough reflex probably as a result of direct depression of the medullary cough centre.

(g) *Vagus* : Morphine stimulates the medullary vagal nucleus and induces bradycardia. This effect, however, is negligible with therapeutic doses.

(h) *Spinal cord* : Morphine is claimed to increase the reflex excitability of the spinal cord by a strychnine like action. This action is, however, usually masked by the depression of the higher centres in the central nervous system. Therapeutic doses of morphine may produce a significant increase in the cerebrospinal fluid pressure.

(i) *Miscellaneous* : Morphine produces a release of ADH with resultant decrease in the urinary output. Administration of morphine reduces the efficacy of diuretics in patients with congestive cardiac failure.

Gastrointestinal tract : Morphine induces vigorous spasm of the smooth muscle of the gut, the ileocolic and the anal sphincters, while at the same time it reduces the propulsive peristaltic movements. Spasmogenic action of morphine is particularly evident in the duodenum and the large intestine. There is a reduction in the secretion of saliva, gastric hydrochloric acid and the intestinal secretions. A prolonged sojourn of the gastrointestinal contents within the bowel lumen leads to an increased absorption of water. Desiccation of the faeces, abolition of the peristaltic movements, spasm of the sphincters, particularly the anal sphincter, and inattention to normal sensory stimuli from a loaded rectum as a result of the psychological effect of morphine, all lead to constipation. Atropine partially antagonizes the spasmogenic action of morphine on the human colon but fails to initiate the propulsive movement abolished by morphine.

Morphine in therapeutic doses produces an increase in the intrabiliary pressure by producing a spasm of the sphincter of Oddi. Hence, although it may relieve the biliary colic because of its analgesic action, the underlying disease is exacerbated. This action, however, does not occur in all subjects. Atropine partially antagonizes this action.

In mice, morphine produces a severe spasm of the anal sphincter resulting in erection of the tail. This test, termed *Straub's test*, was formerly employed to detect morphine in biological fluids but many other compounds including methadone evokes a similar response.

Other smooth muscles : Morphine produces an increase in the tone of the ureters and the detrusor muscle of the bladder. The vesical sphincter is contracted. These effects are augmented by inattention to stimuli arising from the bladder and may result in urinary retention.

Morphine increases the tone of the bronchi and the bronchioles. Except in large doses, it has no significant effect on the normal human uterus at full term.

Cardiovascular system : Therapeutic

doses of morphine have negligible effect on blood pressure or the heart. Toxic doses of morphine may induce hypotension. Morphine produces dilatation of the peripheral blood vessels, particularly the capillaries, partly by a direct effect and partly through release of histamine and may thus cause flushing and fall of blood pressure. Pruritus and sweating often accompany flushing.

Metabolism : Morphine decreases the metabolic rate resulting in a slight fall in body temperature. Reduced respiratory rate, decreased muscular activity and peripheral vasodilatation all contribute towards reduction in the body temperature.

Absorption, fate and excretion : The absorption of morphine given orally is slow and incomplete. Because of extensive hepatic biodegradation, its bioavailability on oral administration is about 20-40%. Given subcutaneously, it produces a demonstrable analgesic effect within 15 to 20 minutes. The peak effect occurs after 60 to 90 minutes. The effect persists for 3 to 5 hours. Considerable amounts of the drug are metabolized during first pass through the liver. Given intravenously, it produces an immediate action.

Morphine circulates in the plasma partly bound to plasma proteins and partly in the free form. Because of its low lipid solubility, it crosses the blood brain barrier inefficiently; that it works so well is because it is such a good agonist. It crosses the placental barrier readily and is also secreted in milk.

Morphine is conjugated with glucuronic acid. Small amounts of free morphine and large amounts of conjugated morphine are excreted in urine. Approximately 90 per cent of the administered dose is eliminated in urine within 24 hours although small amounts are detectable in urine upto 48 hours. Biliary excretion of the conjugated form accounts for approximately 7 to 10 per cent of the administered dose; this amount appears in faeces. Small amounts of the drug are excreted in the sweat.

Preparation and dosage :

(i) Tincture opium I.P. : is a hydro alcoholic solution containing 10 per cent opium and 1 per cent morphine W/V. Dose : 0.3 to 2.0 ml. by

mouth.

(ii) Chlorodyne : This is a chloroform and morphine tincture containing 0.229 per cent of morphine hydrochloride. Dose : 0.3 to 0.6 ml.

(iii) Morphine solutions (2-20 mg/ml) are available for oral use. Oral dose in adults is 10-30 mg. Oral administration is only about one sixth as effective as parenteral administration.

(iv) Morphine hydrochloride or sulfate injection I.P. Each ampoule contains 10 mg of the salt in water for injection. Dose : 10-20 mg s.c. or i.m.; 2.5-5 mg i.v. slowly over 5 minutes. It has also been used by a continuous, low dose, intravenous infusion and by epidural and intrathecal administration. If given by I.V. infusion, 10 mg are infused over the first 1 hour and another 10 mg over the next 4 hours.

(v) Controlled release capsules (10, 30 and 60 mg) of morphine sulfate for prolonged action are now available.

Adverse reactions : By its pharmacological actions, morphine can produce a variety of adverse effects like dysphoria, constipation, dryness of mouth, mental clouding, vertigo, nausea and vomiting, headache, fatigue, paraesthesiae and increased pressure in the biliary tract. Development of constipation following morphine may be dangerous in old people as it may precipitate intestinal obstruction. The drug may also cause abdominal distension. The other important adverse reactions are :

(a) **Intolerance :** With therapeutic doses, morphine may occasionally produce tremors and delirium. Other manifestations include allergic skin rashes, pruritus and contact dermatitis. Morphine is a histamine liberator. Anaphylactoid reaction with fall in blood pressure has been occasionally reported after morphine injection.

(b) **Acute morphine poisoning :** Acute morphine poisoning may occur from clinical overdosage, accidental overingestion in an addict or from suicidal or homicidal intention. It is difficult to define the toxic and the lethal doses of morphine. A dose of 60 mg. is usually toxic but rarely fatal in a normal adult who is not in pain. Doses of 250 mg. are usually fatal. Larger doses

are generally required to produce toxicity in individuals with pain, whereas in addicts, the toxic as well the fatal doses are much higher. Morphine poisoning is characterised by respiratory depression, pinpoint pupils, cyanosis, reduced body temperature and urinary output, hypotension, shock and coma. Convulsions may occur in infants. Death is usually due to respiratory depression or as a result of shock, pulmonary edema and secondary infection.

In principle, morphine poisoning is treated on similar lines as acute barbiturate intoxication. If a toxic dose of morphine has been ingested, even late gastric lavage is justified as the spasmogenic action of morphine frequently delays its absorption.

Unlike with barbiturates, the actions of morphine can be antagonised by specific antagonists naloxone and nalorphine. These drugs produce dramatic reversal of morphine-induced respiratory depression. Naloxone is usually preferred because of its specific antagonistic and negligible agonistic action. It is given intravenously in the dose of 0.4-0.8 mg. repeated every 10-15 minutes. Doses upto 10 mg. have been given. For children, the initial dose is 0.01 mg/kg. If no effect is observed after 2-3 doses, the accuracy of the diagnosis should be checked. Nalorphine is usually administered intravenously in the dose of 3 to 5 mg., repeated within half an hour if necessary. Opioid antagonists should be administered with caution in treating acute morphine poisoning in addicts as they may produce a severe withdrawal syndrome. The duration of action of opioid antagonists is shorter than that of opioids and the patient has to be carefully watched to prevent re-development of coma

(c) **On the foetus :** Morphine administered to the mother during labour cross the placental barrier and may produce depression of foetal respiration. This asphyxia can be reversed by injection of 0.1 to 0.2 mg. of nalorphine or 0.05 to 0.1 mg. of levallorphan in the umbilical vein of the newborn.

(d) **Hypotension :** Morphine occasionally produces hypotension as a result of peripheral

vasodilatation. Patients with reduced blood volume are more susceptible to the hypotensive effect of morphine.

(e) Morphine may produce urinary retention in old people with prostatic hypertrophy by producing a spasm of the sphincter.

(f) **Tolerance :** Repeated administration of morphine results in the development of tolerance. With intermittent use of morphine, however, it is possible to obtain the desired analgesic and sedative effects with the same dose. Tolerance develops to the respiratory depressant, analgesic, sedative and euphoriant effects of morphine as well as to urinary retention, *but the pupils and the gastrointestinal tract do not share this tolerance.* A morphine addict thus has characteristically pinpoint pupils and is habitually constipated. Unlike in the case of barbiturates, development of tolerance greatly alters the lethal dose of morphine and an addict can survive enormous doses of morphine.

Tolerance to morphine is attributed primarily to the ability of the cells of the central nervous system to withstand large doses of the drug.

Persons tolerant to morphine usually exhibit cross tolerance to other opioid analgesics and even to compounds like barbiturates and alcohol.

(g) **Drug dependence :** This is a major drawback of morphine therapy. Opium has been in use as a drug of addiction for several centuries and has precipitated wars. Morphine addiction results mainly from its euphoriant effects. In addition, morphine produces a variety of sensations such as a 'turning in the stomach', a feeling of warmth in the epigastrium and other parts of the body due to flushing and sensations in the lower abdomen described by addicts as akin to sexual orgasm, and known as "kick" or "thrill".

Morphine addicts are usually malnourished and debilitated. Even though they do not suffer from motor incoordination and are capable of performing complex motor and intellectual tasks, the productivity and the utility of the individual to the society usually suffer. As the drug is commonly self injected in a large number of addicts, the

incidence of injection abscesses, tetanus and serum hepatitis is high. Due to depression of libido, marital conflicts are common and economic distress may often lead to suicidal tendency.

The withdrawal syndrome appears after an abstinence period of 6 to 12 hours after the last dose and can be very severe and even fatal. The person develops intense craving for the drug, lethargy and weakness. After 12 hours, yawning, lacrimation, perspiration, rhinorrhoea, tremors and anorexia appear. The peak of the abstinence syndrome is reached after 48 hours and is characterised by fever, rise in blood pressure, increase in heart rate, dilatation of previously constricted pupils and abdominal cramps. Nausea, vomiting, diarrhoea and anorexia may result in severe dehydration, prostration and cardiovascular collapse. The signs and symptoms of abstinence syndrome disappear within 7 to 10 days but the patient may complain of restlessness, insomnia, weakness, back and leg pains for several weeks. The mechanism of opiate withdrawal syndrome is not known but the involvement of neurotransmitter noradrenaline is suspected.

In order to prevent morphine addiction, morphine should not be prescribed readily for chronic pain except in cases of terminal cancer pain. At the same time, however, it is not justifiable to withhold morphine from an advanced case of malignancy with excruciating pain.

The treatment of morphine dependence, in principle, is similar to that of alcohol or barbiturate dependence. The results, however, are unsatisfactory because of the severity of withdrawal syndrome and the high relapse rate. Gradual withdrawal of morphine with substitution of another opioid analgesic to decrease the severity of withdrawal syndrome is usually advocated. Methadone is often used for replacement as it can be administered orally and has a longer duration of action than morphine. One milligram of methadone will substitute for 4 mg of morphine. Once the patient is stabilized on methadone, its dose is gradually reduced by 20 per cent daily and the drug can be completely stopped from 6th to 10th

day.

Acute opiate withdrawal symptoms and signs can be controlled to a certain extent by drugs like chlorpromazine, propranolol and clonidine which counter the noradrenergic function.

Therapeutic uses of morphine :

(i) **For relief of pain :** Morphine is one of the most powerful analgesics. It is employed to alleviate severe pain in conditions such as acute myocardial infarction, fractures of long bones, burns, terminal stage of malignancy, pulmonary embolism, acute pericarditis, pleurisy with effusion and spontaneous pneumothorax. For relief of sudden excruciating pain, morphine is usually administered intravenously; it produces prompt relief of pain and thus minimises shock. Subcutaneous administration of morphine is not advocated in the presence of shock, as its absorption is hampered. Repeated subcutaneous administration of morphine under these conditions may result in a sudden absorption of toxic quantities into systemic circulation after the correction of hypotension.

Morphine can be used for relief of pain in renal and biliary colic. However, it is always combined with atropine which produces smooth muscle relaxation and thus helps to relieve spasm.

Parenteral morphine has been used to reduce post-operative pain; thoughtless use for this purpose should be avoided as it can produce respiratory depression, urinary retention and constipation; it reduces coughing and may mask the signs of recovery and of complications.

Since opiate receptors are located within the spinal cord, intrathecal and epidural morphine has been used to produce analgesia. Such analgesia is essentially segmental in distribution, the pain relief being remarkable for its specificity without any interference with motor function or autonomic changes. The typical adverse effects of systemic opiates are rare. The use of hyperbaric morphine solution probably minimizes the risk of adverse effects. Such analgesia can last upto a few days. Because of greater safety and ease of ad-

ministration, most investigators prefer the epidural route to intrathecal route.

(ii) **Sedation and sleep** : Morphine is a valuable sedative in the presence of pain. As it does not affect the uterine motility, it has been used as a sedative in threatened abortion.

Although, morphine has been used routinely for sedating patients with internal bleeding such as haematemesis, a tranquillizing drug, like diazepam might be safer for this purpose.

(iii) **As preanaesthetic medication** : See Chapter 5.

(iv) **In acute left ventricular failure** : Morphine is valuable in the treatment of acute left ventricular failure and pulmonary edema. It acts by reducing apprehension and the effort of breathing. Evidence indicates that morphine induced peripheral vasodilatation results in shunting of the blood from the pulmonary arteries to the dilated peripheral vasculature and this, in turn, reduces pulmonary artery blood flow, pulmonary artery pressure and central venous pressure. Thus, it reduces the cardiac work, provided oxygenation is maintained.

(v) **To produce constipation** : Tincture opium (0.5 to 1 ml) and paregoric are sometimes used for symptomatic relief of severe diarrhoea.

(vi) **Miscellaneous** : Morphine is not recommended for suppressing cough because of many disadvantages (see Chapter 22). In the dose of 1-3 mg/kg. intravenously, it has been used, alone or in combination with other drugs, to produce general anaesthesia especially in subjects who are considered as bad anaesthetic risks.

Precautions with morphine therapy:

(i) Morphine should be administered with caution to persons with diminished respiratory reserve e.g. individuals with emphysema, kyphoscoliosis and chronic obstructive lung disease. Such patients are already on the verge of hypoxia which they avert by increasing their respiratory rate. Morphine and other opioids decrease ciliary activity, depress cough reflex, increase bronchomotor tone and depress respiration, all of which

can precipitate respiratory failure in such individuals. Deaths have been reported in patients with chronic obstructive lung disease following therapeutic doses of morphine.

(ii) The lowered basal metabolic rate in myxoedema makes such patients more sensitive to opioids and sedatives and frank coma may be precipitated by even conventional therapeutic doses of these drugs. Patients with hypopituitarism and Addison's disease are also more sensitive to morphine.

(iii) Phenothiazines, monoamine oxidase inhibitors and tricyclic antidepressants enhance the sedative effects of morphine and increase the respiratory depression.

(iv) Morphine may produce hypotension if administered during hypovolemic shock. *It is more important to restore circulating blood volume than administer morphine in hypovolemic shock.*

(v) Old people and infants are more prone to develop respiratory depression with morphine.

(vi) Morphine produces an increase in the cerebrospinal fluid pressure, stimulates the spinal cord and produces respiratory depression, vomiting and miosis. Miosis and mental clouding produced by morphine may interfere with the diagnosis. Hence, morphine should be avoided in cases with head injuries.

(vii) **Acute abdomen** : Morphine relieves pain without modifying the underlying pathological process. It interferes with the diagnosis by masking pain and creates a false sense of security. Morphine induced vomiting and its spasmogenic action on the gastrointestinal and biliary tract are additional drawbacks. It may, however, be administered after the diagnosis has been established.

(viii) Cumulative toxicity can occur in patients with severe impairment of liver and/or kidney function.

Other phenanthrene alkaloids of opium:

CODEINE : Codeine is a much less potent analgesic than morphine. It does not produce sig-

nificant depression of respiration and has a low addiction liability. In toxic doses, however, it may produce excitement and convulsions. It enhances the analgesic effect of salicylates and is often combined with them. Unlike morphine, it is much better absorbed when given orally and its bioavailability on oral administration is about 50%. Hence, it is most commonly used as an antitussive and is discussed elsewhere in detail. Codeine phosphate is available for oral and intramuscular use. Dihydrocodeine and oxycodone are other drugs used for similar purposes as codeine (See Chapter 22).

Benzylisoquinoline alkaloids of opium:

PAPAVERINE : Papaverine in therapeutic doses is devoid of opioid and analgesic activity. It has, however, a relaxant action on the smooth muscles. It has been employed mainly as a coronary dilator and in peripheral vascular disease. These uses are discussed elsewhere. Intracavernosal injection of papaverine causes penile erection and the drug has been employed by this route for symptomatic treatment of impotence. This procedure, however, can cause complications.

NOSCAPINE: This alkaloid has significant antitussive action in therapeutic doses, without other disadvantages of morphine. Its application in the pharmacotherapy of cough is discussed in Chapter 22.

SEMISYNTHETIC DERIVATIVES OF NATURAL OPIUM ALKALOIDS

Codeine derivatives are mainly antitussive and are discussed elsewhere. Only the derivatives of morphine will be discussed here. These are:

HEROIN (Diacetylmorphine) : It is a more powerful analgesic than morphine, produces greater euphoria and consequently has a higher addiction liability. It is rarely employed therapeutically because of this drawback.

The newborn children of mothers who are heroin addicts have been known to develop a

'withdrawal syndrome' a few hours after birth. The treatment of heroin addiction is similar to that of morphine addiction; one mg. of methadone can substitute for 2 mg. of heroin.

Dihydroxymorphinone (Dilaudid), oxymorphone (Numorphan) and methyldihydro-morphinone (Metopon) in the doses of 1.5 mg., 1.5 mg., and 3.5 mg. respectively are effective analgesics with 4-5 hours of duration of action. Their toxicity is similar to that of morphine.

APOMORPHINE: This drug is obtained by the acid-catalyzed rearrangement of morphine. It is a stimulant of CTZ situated in the area postrema and acts as potent emetic. The emesis is due to activation of dopaminergic (DA) receptors which in turn stimulate an emetic centre located in the area of the nucleus fasciculi sediterrii. The effect is blocked by neuroleptics like chlorpromazine but not by antihistaminic agents, even in large doses. The drug also produces, in threshold doses, an increase in exploratory activity and discontinuous sniffing in rats. Larger doses cause purposeless behaviour characterized by continuous sniffing, grooming, biting and licking, described as '*stereotyped behaviour syndrome*'. In cats and dogs, it causes side to side head movements and incessant running around the cage. These effects are also blocked by neuroleptics and are due to direct stimulation of DA receptors located in the neostriatum. The drug acts on both pre- and post-synaptic DA receptors and thus produces a variety of behavioural, neuropharmacological and endocrine effects. In man, a subcutaneous dose of 0.1 mg/kg ordinarily causes vomiting within a few minutes. Adverse reactions include nausea, vomiting, dizziness, hypotension and bradycardia. The drug is of great pharmacological interest (See Chapter 37).

SYNTHETIC MORPHINE SUBSTITUTES

These are :

- (A) Pethidine and its congeners
- (B) Methadone and its congeners
- (C) Morphinan compounds and congeners e.g.

levorphanol and butorphanol

(D) Benzomorphan derivatives e.g. pentazocine

(E) Miscellaneous : nalorphine, buprenorphine.

PETHIDINE (Meperidine, Demerol) :

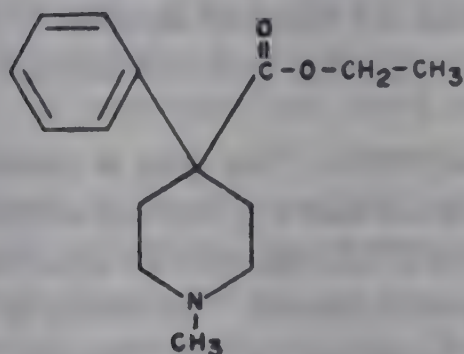


Fig. 8.2 Pethidine

Pharmacological actions : As the pharmacological actions of this synthetic opioid closely resemble those of morphine, only the salient differences between these two compounds will be pointed out. Thus,

(a) On weight basis, it is about 1/10th as potent as morphine as an analgesic, when given intravenously. The mechanism of analgesia is the same as with morphine.

(b) In equianalgesic doses, pethidine produces as much sedation, euphoria and respiratory depression as morphine. However, unlike morphine, it reduces the tidal volume without significantly affecting the respiratory rate. Therefore, respiratory depression may be missed if respiratory rate alone is watched. Retention of carbon dioxide produces cerebral vasodilatation and increases the cerebrospinal fluid pressure.

(c) After systemic administration pethidine produces corneal anaesthesia and thus inhibits the corneal reflex. In contrast to morphine, pethidine does not constrict the pupils.

(d) Pethidine is devoid of significant antitussive activity. The incidence of nausea and vomiting following pethidine is higher than with morphine. It also reduces the urinary output.

(e) Pethidine exerts a vagolytic action on the

isolated intestinal strip but usually produces *in vivo*, spasm of the smooth muscle of the bowel wall and sphincters. It also raises intrabiliary pressure by producing spasm of the sphincter of Oddi.

(f) Pethidine may occasionally produce hypotension and syncope due to peripheral vasodilatation. Unlike morphine, however, intravenous pethidine administration occasionally produces tachycardia by virtue of its vagolytic effect.

Absorption, fate and excretion : Unlike morphine pethidine is satisfactorily absorbed from the gut with a bioavailability of about 50%. On oral administration, the analgesic effect appears within 10 to 15 minutes and persists for several hours while on parenteral administration the action lasts for 2 to 4 hours as compared to 3 to 5 hours with parenteral morphine. Pethidine crosses the placental barrier and is also secreted in milk. It is mainly metabolized by the liver; the metabolic product norpethidine possesses significant excitatory action on the central nervous system. Norpethidine tends to accumulate during chronic use. Only a small portion is excreted unchanged in the urine. The urinary excretion of the drug is enhanced when the urine is acidic.

Preparations and dosage : Pethidine hydrochloride tablets I.P. contain 50 mg. of the salt. Dose : 25 to 100 mg. for analgesia. Pethidine hydrochloride injection I.P. is available as 2 ml. ampoules containing 50 mg. per ml. of the salt. Dose : subcutaneous or intramuscular 25 to 100 mg. Intravenous : 25 to 50 mg.

Adverse reactions : (i) The adverse effects apart from local irritation on parenteral administration, include sweating, euphoria, dizziness, dry mouth, vomiting, dysphoria, visual disturbances, weakness and palpitation. Anaphylactic shock following intramuscular administration of pethidine has been reported.

(ii) Pethidine administered to mothers in the dose of 50 mg. I.M. within 2 hours before childbirth produces significant depression of foetal respiration. However, such an effect is not demonstrable when the drug is administered within

1 hour before childbirth. A larger dose tends to increase foetal asphyxia.

(iii) Pethidine, when administered along with promazine parenterally, may produce circulatory collapse while its administration to patients receiving a monoamine oxidase inhibitor may result in confusion, cerebral excitement and collapse. A similar effect has been reported in patients receiving imipramine.

(iv) It is capable of producing bronchospasm and has a tendency to produce drying of secretions. It also produces respiratory depression and hence, contrary to popular belief it is not a suitable drug in patients with bronchial asthma.

(v) Overdosage with pethidine may produce respiratory depression and coma or tremors and convulsions. Nalorphine can antagonize the respiratory depression and coma but fails to modify the convulsant action of pethidine. Acute pethidine poisoning should be treated on similar lines as acute morphine poisoning.

(vi) Tolerance to analgesic and emetic effects develops on prolonged administration. The pethidine addict often shows dilate pupils, tremors, mental confusion, twitchings and occasionally convulsions.

(vii) Phenytoin increases the biodegradation of pethidine. Cimetidine (but not ranitidine) reduces the clearance of pethidine (but not morphine). Thus, morphine is a safer drug than pethidine to use in patients who are on cimetidine.

Addiction to pethidine is fairly common, especially in the medical profession. The withdrawal syndrome usually develops within 3 hours after the last dose, reaches peak by 8 to 12 hours and declines by 4 to 5 days. There is little nausea, vomiting or diarrhoea but the patient may show more excitement than during morphine withdrawal. The treatment of pethidine addiction is similar to that of morphine addiction. Methadone is employed initially as a substitute. One mg. of methadone can substitute for 20 mg. of pethidine.

Contraindications to the use of pethidine are similar to those for morphine.

Therapeutic uses,

(i) **Analgesia** : It is particularly useful when

short duration of action is required, as in gastroscopy, cystoscopy or ascending pyelography. Pethidine serves as a morphine substitute for relief of acute visceral pain e.g. in myocardial infarction, particularly those associated with bradycardia and in burns. The precautions observed with morphine administration for the treatment of shock also apply to pethidine.

Like morphine, epidural and intrathecal pethidine (10-30 mg) produces local analgesia.

As the active metabolite norpethidine tends to accumulate and might cause toxicity during long term use of pethidine, morphine and methadone are to be preferred for such purpose.

(ii) **Preanaesthetic medication** : Discussed in Chapter 5.

(iii) **Obstetrical analgesia**: As pethidine does not interfere with uterine contractility, it is often used for this purpose in minor procedures like dilatation and curettage.

PETHIDINE CONGENERS: These are piminodine, phenoperidine, fentanyl (see Chapter 5), anileridine, diphenoxylate (see Chapter 37), and alphaprodine. The first four do not offer any remarkable advantage over pethidine except reduction of dosage. Diphenoxylate is used in the treatment of diarrhoea and in therapeutic doses it does not produce morphine-like subjective effects; large doses, however, cause typical opioid symptoms. Alphaprodine has a shorter duration of action (one half to two hours) on subcutaneous administration and causes emesis less frequently than other opioid analgesics. It is administered orally or parenterally in the dose of 40 to 60 mg. It has been used for relief of pain in the first stage of labour. Loperamide, a piperidine derivative, is used for its constipating action (See Chapter 38).

METHADONE (Physeptone): Methadone is a synthetic compound with analgesic potency equivalent to or slightly greater than that of morphine.

Pharmacological actions : These are more or less similar to those of morphine. A single therapeutic dose exerts much less hypnotic activ-

ity than an equianalgesic dose of morphine. The drug depresses respiration to the same degree as morphine and has a marked antitussive effect. The actions of the drug on the gastrointestinal tract and the cardiovascular system are similar to those of morphine.

Absorption, fate and excretion: Unlike morphine methadone is satisfactorily absorbed from the gastrointestinal tract, with a bioavailability of about 80%. The analgesic effect occurs within 10 to 15 minutes following parenteral and 20 to 30 minutes after oral medication. Peak plasma levels are reached within 1 to 2 hours after parenteral administration. Given intravenously, it is as potent as morphine. It has a longer duration of action than morphine. It crosses the placental barrier.

Methadone is mainly metabolized in the liver. Less than 10 per cent of the drug is excreted unchanged by the kidneys.

Preparations and dosage: Methadone hydrochloride tablets I.P., 5 mg. tablets. Dose : 5 to 10 mg.

Methadone hydrochloride injection I.P., ampoules containing 5 mg. of the salt per ml. Dose 5 to 10 mg. by subcutaneous injection. Intravenous injection should be given slowly and with patient in recumbent position to avoid syncope.

Adverse reactions : The adverse effects include dizziness, nausea, vomiting, sweating, mental clouding, dryness of mouth and constipation. Methadone may produce irritation on parenteral injection and its repeated administration can result in cumulative toxicity. Methadone shares the respiratory depressant action of morphine. Acute methadone intoxication responds to naloxone and should be treated on similar lines as morphine intoxication.

Tolerance develops to the central nervous system depressant and cardiovascular effects of methadone. The development of tolerance, however, occurs more slowly than with morphine. Addiction liability of methadone is less than that of morphine; the withdrawal syndrome develops more slowly and is less intense. The

symptoms, however, persist for a much longer time, approximately 10 to 15 days. Codeine is often used as a substitute during treatment of methadone addiction.

Therapeutic uses : The oral effectiveness of methadone, its analgesic potency and lack of marked hypnosis make it a useful drug for the management of chronic pain. Further, it can be used as a substitute for morphine, heroin and pethidine for relief of severe visceral pain and in the treatment of opioid abstinence syndrome.

As an antitussive, codeine is preferred to methadone owing to the higher addiction liability of the latter.

METHADONE CONGENERS : These are dipipanone and propoxyphene. The former, administered in the dose of 15 to 25 mg. subcutaneously, produces more sedation than methadone. **Propoxyphene** (Darvon) has been claimed to produce less depression of respiration, and gastro-intestinal side effects. In fact, the drug retains only minimal pharmacological properties of opioid analgesics and yet has significant addiction liability. As an analgesic, it is only $1/25$ - $1/50$ th as potent as morphine and is $1/2$ as potent as codeine. Sixtyfive mg of propoxyphene hydrochloride is no more effective than 650 mg of aspirin. It has no antitussive action. It is administered orally in the dose of 250 mg per day in divided doses. It can cause respiratory depression and has abuse potential. The drug has little advantage over codeine.

MORPHINAN COMPOUNDS : The compound levorphanol is a more potent analgesic than morphine, is better absorbed on oral administration and produces less constipation. The addiction liability of this compound is similar to that of morphine. It is administered orally or subcutaneously in the dose of 2 to 3 mg.

BUTORPHANOL: is a morphinan congener with properties similar to those of pentazocine. Its agonist activity (on weight basis) is 4-7 times that

of morphine and it is 20 times as potent as pentazocine. It is administered i.m. or i.v. in the dose of 2 mg.

PENTAZOCINE (Fortral, Fortwin) : This benzomorphan derivative has potent analgesic (agonist) and a weak opioid antagonist activity. Compared to opiates it has a low dependence liability. It does not cause euphoria. As an analgesic, it is about half as effective as morphine, and can cause respiratory depression, though less than morphine. Unlike morphine, it raises the systemic and pulmonary arterial blood pressures with resulting increase in cardiac load. Further, it has shorter duration of action than morphine. Hence, it is not recommended in myocardial infarction.

Absorption, fate and excretion : Pentazocine is given orally, rectally and parenterally. Although it is well absorbed orally, only 20% is bioavailable due to first pass metabolism. It is extensively metabolised by the liver and is excreted as glucuronide. Smokers metabolise 40% more pentazocine than non-smokers.

Adverse reactions: These include sedation, sweating, dizziness and nausea. The drug sometimes causes psychomimetic reactions, hallucinations and unpleasant dreams. This is an important limitation to its use. Given in narcotic addicts it acts as a narcotic antagonist and may precipitate an acute withdrawal syndrome. Prolonged parenteral use may cause sterile abscesses and fibrous myopathy. Nalorphine is valueless as an antidote to pentazocine but naloxone is useful. Tolerance and physical dependence have been reported though the incidence is low.

Miscellaneous:

NALBUPHINE : This synthetic compound is chemically related to oxymorphone and the opioid antagonist naloxone. It has both agonist and antagonist properties. As an agonist, it is 3-4 times more potent than pentazocine while its antagonistic property is about 10 times more than that of pentazocine. The adverse effects are

similar to those of pentazocine. It is less suitable than morphine for management of severe pain. It probably causes fewer psychotomimetic effects and has less potential for abuse than pentazocine. Further its adverse hemodynamic effects are less than pentazocine.

BUPRENORPHINE: Thebaine, an opium alkaloid, is a convulsant and has no therapeutic application. Buprenorphine, a semisynthetic derivative of thebaine, has both opioid agonist and antagonist properties. As an analgesic, it is 25-30 times more potent than morphine on weight basis and has longer duration of action. When it is given following induction of anaesthesia with nitrous oxide and fentanyl, it reverses the anaesthetic and respiratory depressant effects of fentanyl but prolongs the analgesia. It has similar cardiovascular actions like morphine in equianalgesic doses and has been used in myocardial infarction. It has less abuse potential than even codeine. This needs confirmation. Naloxone does not precipitate withdrawal symptoms as it does with other opioid analgesics.

Absorption, fate and excretion : It can be given orally, sublingually and parenterally. Bioavailability after sublingual administration is about 50%. The drug is highly protein bound. The drug is excreted unchanged mainly in the faeces, and in smaller amount in the urine.

Adverse effects : Like other opioid analgesics, it can cause respiratory depression similar to morphine at equianalgesic doses. However, unlike morphine, the action is not readily reversed by naloxone. Doxapram, a respiratory stimulant, may be useful. Other adverse effects are drowsiness, nausea, vomiting, constipation, miosis, bradycardia and hypotension. It is administered in doses of 0.3-0.6 mg every 6-8 hourly, sublingually or intramuscularly.

OPIOID ANTAGONISTS

(Drugs that antagonize the effects of morphine and other opioid analgesics act mainly by competitive antagonism. In addition, some of them also exert

other actions not related to morphine receptors. Depending upon their differing actions they are classified as :

- (1) Pure antagonist such as Naloxone.
- (2) Partial agonists of Nalorphine-type e . g . Nalorphine, Levallorphan and Cyclazocine, and
- (3) Partial agonists of the Morphine-type e.g. Propiram and Profadol. In man drugs from this group produce similar agonistic actions as morphine, which are antagonized by nalorphine or naloxone. However, they precipitate withdrawal symptoms in subjects maintained on high doses of morphine.

NALOXONE (Narcan): This drug, N-allyl analogue of oxymorphone, selectively antagonizes the respiratory depressant action of morphine and other opioids. Given orally, it is only 1/50 as potent as when given parenterally because of its metabolism in the liver. One mg of naloxone given intravenously completely blocks the effects of 25 mg of heroin. Its duration of action is 3-4 hours. By itself, it is not a respiratory depressant, analgesic or euphoriant; it is thus a pure antagonist. It is almost completely metabolized in the liver. During prolonged administration, tolerance to the opioid antagonist properties does not occur. No abstinence syndrome develops on withdrawal of this drug. Interestingly, it reduces the severity of abstinence syndrome on withdrawal of morphine and heroin.

It is available in vials containing 0.4 mg/ml. and is considered as the antagonist of choice in the treatment of opioid poisoning. It is also used to reverse the residual respiratory depressant effects of an analgesic at the end of operative procedure.

Endogenous opioid peptides are released by stress and may be responsible for hypotension observed in shock. Naloxone, given I.V., has been reported to correct the hypotension observed in septicæmic shock, though the effect is short lived.

NALORPHINE (N-allyl normorphine): Nalorphine is a semi-synthetic congener of morphine produced by replacement of the methyl radical attached to the nitrogen in morphine by an allyl group. It is used mainly in the treatment of acute morphine poisoning.

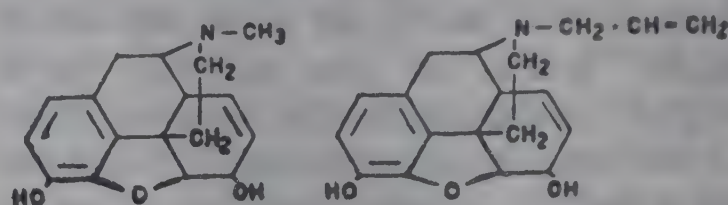


Fig . 8.3: Morphine

Nalorphine

Pharmacological actions:

(i) When administered to humans without prior medication with morphine, nalorphine in therapeutic doses exerts significant analgesic effect comparable to that of morphine. Nalorphine analgesia is accompanied by drowsiness and relaxation but a large number of patients experience dysphoric symptoms such as anxiety, confusion, disorientation, visual hallucinations and malaise and these make the use of this compound as an analgesic impractical.

Nalorphine shares many other pharmacological actions of morphine. Thus, it exerts spasmogenic activity on the smooth muscle of the gut wall and the sphincters, has a demonstrable antitussive effect and in large doses, produces nausea, vomiting, miosis, sweating, flushing and pallor of the skin. Large doses also induce respiratory depression and increase the cerebrospinal fluid pressure. However, unlike morphine, nalorphine does not produce drug dependence, nor does it support physical dependence of morphine-type.

(ii) When administered after morphine or its semisynthetic derivatives, nalorphine promptly abolishes euphoria, analgesia, drowsiness, respiratory depression, miosis, muscular incoordination, vomiting, spasm of the smooth muscle and sphincters of the gastrointestinal and the biliary tract produced by these drugs. Nalorphine, however, enhances the antitussive effect of morphine.

Nalorphine is also a potent antagonist of codeine, semisynthetic derivatives of morphine like heroin and synthetic morphine substitutes like pethidine and methadone. *However, it is much less effective against pethidine than against the other opioid analgesics.*

Nalorphine is not a respiratory stimulant and in man, it fails to antagonize respiratory depression produce by alcohol and barbiturates and may even add to their depressant effect.

(iii) When administered to a morphine addict in the dose of 1 to 3 mg., nalorphine precipitates the typical withdrawal syndrome of morphine abstinence. The withdrawal syndrome appears within 3 to 15 minutes, reaches a peak by 45 minutes and disappears within 2 hours. Another test to diagnose an addict is to observe the pupils. In normal individuals nalorphine produces miosis but in an addict, it either dilates the pupils or fails to produce any demonstrable effect on the pupils.

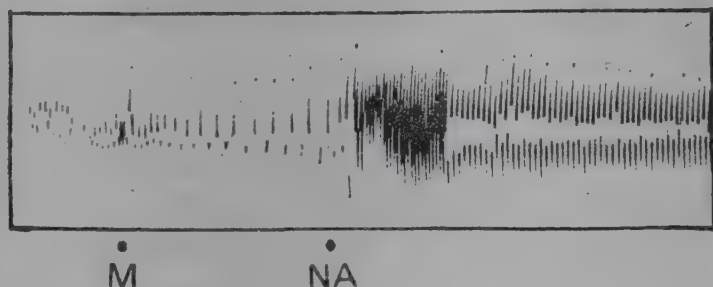


Fig. 8.4: Effect of nalorphine (NA) on morphine (M) depressed respiration in anaesthetized cat.

Nalorphine precipitates withdrawal syndrome in patients addicted to heroin and methadone. However, it does not produce withdrawal syndrome in pethidine addicts unless the amount of pethidine ingested daily exceeds 2 g.

The mechanism of morphine-nalorphine antagonism is not definitely elucidated. However, it is postulated that nalorphine acts as a partial agonist, and produces analgesia and respiratory depression. When administered after morphine, it displaces morphine from the receptor sites (competitive antagonism) within the central nervous system, thereby reversing the effects of morphine.

Absorption, fate and excretion: Nalorphine is poorly absorbed from the gastrointestinal tract. It is absorbed more rapidly than morphine

on subcutaneous administration. It is much more effective parenterally than when given orally. Peak plasma levels are reached within 15 to 30 minutes. The drug achieves a higher concentration in the brain than morphine and is mainly detoxified in the liver by conjugation.

Preparations and dosage : Nalorphine injection I.P. (Lethidrone) 10 mg. per ml., administered subcutaneously or intravenously in the dose of 3 to 10 mg. The dose may be repeated to a total of 40 mg.

Therapeutic uses:

(i) Acute poisoning due to morphine and related compounds.

(ii) Diagnosis of morphine addiction.

(iii) Nalorphine has been administered to morphine addicts along with morphine. Withdrawal of the mixture produces a milder withdrawal syndrome than that observed after withdrawal of morphine alone.

LEVALLORPHAN: This is another opioid antagonist similar to but more potent than nalorphine. It is available as ampoules containing 1 mg. of the drug per ml. and is given intravenously in the dose of 0.2 mg. It generally fails to reverse pethidine induced respiratory depression.

CYCLAZOCINE: Cyclazocine is a nalorphine type of opioid antagonist. The compound itself is a potent analgesic and respiratory depressant but cannot be used clinically because of the high degree of tolerance and dysphoria. When administered orally in the dose of 2 mg. twice daily to human volunteers, the drug effectively antagonizes the euphoriant and toxic actions of morphine and prevents the development of physical dependence. The drug is thus useful for the treatment of both acute morphine intoxication and morphine addiction, as its chronic administration along with morphine results in a reduction of the severity of withdrawal syndrome. It is effective orally and has a longer duration of action than nalorphine.

NALTREXONE : This is an orally administered, long acting, pure opioid antagonist. Naloxone is too short acting and is ineffective by mouth. Naltrexone is well tolerated and has no euphoric effect, does not cause physical dependence and consistently blocks the effects of heroin and other addictive opiates for upto four days. For

treating heroin addiction, small initial doses (1-5 mg) given along with clonidine reduce the severity and duration of withdrawal symptoms significantly, compared to clonidine alone. Thereafter, the patient can be given full doses of naltrexone, using a thrice weekly schedule.

9 Analgesic-Antipyretics and Nonsteroidal Anti-inflammatory Drugs (NSAID)

In contrast to the opioid analgesics, the non-opioid analgesics relieve pain without interacting with the opioid receptors; they possess anti-inflammatory property and are known as 'Non Steroidal Anti Inflammatory Drugs' (NSAID). Further, they reduce elevated body temperature (antipyretic effect). They also possess uricosuric property to varying degrees and are non-addicting. These effects are achieved with doses that do not produce significant depression of the central nervous system.

Temperature regulation : Although the *body surface temperature* is ordinarily measured in clinical practice, it is the *body core temperature* which is physiologically important. If the core temperature rises by more than a few degrees in man, mental changes occur. It is well known that an individual with high fever is often confused and delirious. The working of many tissue enzymes is also adversely affected at high temperature and hyperpyrexia may result in fatality.

The hypothalamus plays an important role in thermo-regulatory responses of the body. It controls the body temperature by two mechanisms. The more important of these is cutaneous vasodilatation, the other one being an increase in sweat gland activity through sympathetic cholinergic fibres. Normally, 60 per cent of the body heat loss occurs by radiation, 20 per cent by evaporation of water and the rest by convection and conduction. The commonest manifestation of a change in the core temperature is fever. Many diseases can give rise to fever, the commonest being infection. The increase in temperature is brought about by the hypothalamus which reduces heat loss by peripheral vasoconstriction and increases heat production by shivering. It then regulates the tempera-

ture around the new setting. Our understanding of the neural basis of thermoregulation and fever is still rudimentary. The agents causing such upward resetting of the hypothalamic thermostat seem to be high molecular weight polysaccharides called *pyrogens*, a lipopolysaccharide, which have been isolated from bacteria and leucocytes. Leucocytes produce endogenous pyrogens which are similar or identical to interleukin-1. It is now generally accepted that pyrogens are the circulating initiators of fever and they induce changes in the C.N.S., presumably in the region of the anterior hypothalamus.

The role of fever in the defence reaction is not clear, though increased destruction of certain infective agents at high temperature has been reported. In practice, as with pain, relief from fever with drugs adds to the comfort of the patient. It also impresses the patient and the relatives favourably about the therapeutic capability of the doctor.

Experimental evaluation of anti-inflammatory activity: The three important aspects of inflammation that render themselves readily to measurement are erythema, edema and formation of granulation tissue. Compounds claimed to possess anti-inflammatory activity can be evaluated either by their ability to reduce one or more of these phenomena in an experimentally induced inflammation or by testing their anti-inflammatory activity in experimental arthritis produced in animals.

The commonly employed methods are :

(1) **Erythema assays :** Irradiation of the shaven back skin of a guinea pig with ultra violet light causes erythema which can be reduced by anti-inflammatory agents. Erythema can also be

produced in human beings with certain specific irritants like tetrahydrofurylnicotinate. The anti-inflammatory property of a new agent is assayed by comparing its ability to reduce this reaction, with that of a known anti-inflammatory drug.

(2) **Edema assays** : Anti-inflammatory activity of a drug can also be measured by noting the reduction in edema produced by the local injection of substances like formaldehyde, carrageenin, histamine, dextran and ovalbumin. A modification involves the measurement of leakage of a protein bound marker (Evans blue, ^{131}I) from the circulation into the tissues; the results obtained however, vary considerably from laboratory to laboratory.

(3) **Granuloma assays** : In this group, the 'Cotton wool pellet' and the 'granuloma pouch' are the most commonly used methods. The former involves subcutaneous implantation of weighed cotton wool pellets, impregnated with a 'foreign' material like carrageenin, in rat. This causes localised inflammation. The animals are sacrificed after the drug treatment; the cotton pellets, now encapsulated and heavily infiltrated with connective tissue are removed, dried, weighed and compared with those in animals not given the drug.

In the granuloma pouch assay, an irritant like croton oil diluted with cotton seed oil or air is injected subcutaneously in the rat, usually on its back. After drug treatment the animal is sacrificed, the pouch is dissected, its exudate content is measured and compared with that in control animals.

(4) **Experimental arthritis assays** : Polyarthritis induced in rats by injection of dead tubercle bacilli suspended in liquid paraffin (Freund's mycobacterial adjuvant) is a frequently used method for measurement of anti-inflammatory activity. Kaolin, talc and even mercury have also been injected directly into the joints of rats and pigeons to induce arthritis.

(5) **Miscellaneous** : Localised inflammatory reaction can be produced in rats by intrapleural injection of turpentine or by intraperitoneal

injection of formaldehyde. Ability of the new agent to suppress acute inflammatory reaction to albumin or horse serum in animals previously sensitised to these antigens (Arthus reaction) can also be studied.

The inflamed paw technique and the adjuvant arthritis model (both in rats) are the most successful methods of predicting analgesic activity in man. Paw inflammation and edema are produced by intra-plantar injection of naphthylheparamine or carrageenin.

Classification : The analgesic-antipyretics can be classified as :

- I. The salicylates and their congeners.
- II. The para-aminophenol derivatives e.g. phenacetin, paracetamol.
- III. The pyrazolon derivatives e.g. phenylbutazone and related compounds.
- IV. Indole-acetic acid derivatives : indomethacin, sulindac and tolmetin.
- V. Phenylacetic acid derivatives: diclofenac.
- VI. Propionic acid derivatives : ibuprofen, fenoprofen, naproxen, ketoprofen and pirofen.
- VII. Fenamates e.g. flufenamic acid, mefenamic acid and enfenamic acid.
- VIII. Oxicams e.g. piroxicam.

Compounds belonging to groups V to VIII are called Newer NSAID.

Mechanism of analgesic-antipyretic action : Though these drugs have different chemical structures, they produce qualitatively similar analgesic, antipyretic and anti-inflammatory effects. According to the current unifying concept of NSAID action, during inflammation, pain and fever, arachidonic acid is liberated from phospholipid fraction of the cell membrane; arachidonic acid is then enzymatically converted to prostaglandins (PGs). It is postulated that PGs sensitize blood vessels to the effects of mediators that increase permeability, such as bradykinin, 5-HT and histamine. PGs particularly PGE and PGI produce hyperalgesia associated with inflammation. They sensitize the chemical receptors of the afferent pain endings to other mediators such as bradykinin and histamine. Further, release of PGs

in the CNS may lower the threshold of the central pain circuits. Prostaglandins cause edema, erythema and pain following intradermal injection and headache and vascular pain when infused intravenously in man. Prostaglandins are also involved in the pyretic response in man and PGE might be a final mediator of the CNS fever mechanism. After the injection of pyrogens there is a rise in PGE in the CSF that is prevented by pretreatment with aspirin.

Aspirin and aspirin like NSAID have been shown to inhibit release or synthesis of PGs and thus produce beneficial therapeutic effects. A similar mechanism of action could also explain some of their adverse effects e.g. nephrotoxicity (see later). Aspirin and other NSAID are effective as analgesics only in pathological states or in experimental models where PGs are synthesized locally. Aspirin is ineffective in sharp "stabbing" pain which is caused by direct stimulation of sensory nerves. The quantitative differences in the actions of different PG inhibitors and their propensity to cause adverse reactions may be explained by the differences in the sensitivities of the cyclo-oxygenase (PG synthetase) in different tissues to the various NSAID. For example, the cyclo-oxygenase in the brain is much more sensitive to paracetamol than the cyclo-oxygenase in the blood vessels.

In addition to its conversion to PGs via the cyclo-oxygenase pathway, arachidonic acid is converted via lipo-oxygenase pathway to leukotrienes (see Chapter 21). NSAID cannot inhibit the production of leukotrienes; in fact, by blocking the synthesis of PGs, they may make more arachidonic acid available for synthesis of leukotrienes. This might explain the symptoms of hypersensitivity in some subjects following the ingestion of aspirin and other NSAID.

Although inhibition of PG biosynthesis can explain many of the therapeutic effects of NSAID, other mechanisms may also play an important role. Thus, indomethacin inhibits phosphodiesterase and thus increases the intracellular concentration of cyclic AMP. Cyclic

AMP has been shown to stabilize membranes including lysosomal membranes in polymorphonuclear leukocytes. This prevents the release of enzymes important in the inflammatory response. Further, the anti-inflammatory drugs which are weak PG inhibitors appear to act by inhibiting the activation of T-lymphocytes which are abundant in the inflamed tissues and release lymphokines. (See Chapter 21.) The lymphokines play an important role in mediating inflammation. Aspirin has both properties: PG inhibition and inhibition of T-lymphocyte activation and of their ability to release lymphokines.

I. SALICYLATES

Salicylates are esters or salts of salicylic acid e.g. methyl salicylate, sodium salicylate or alternatively, can also occur as salicylate esters of organic acids such as acetyl salicylic acid (aspirin). A compound which resembles the salicylic acid esters is salicylamide.



Fig. 9.1 : Aspirin

Sodium Salicylate

Pharmacological actions of salicylates :

Local actions : Salicylic acid and methyl salicylate are irritants and have keratolytic, anti-septic and fungistatic actions (see Chapter 57).

The salts of salicylic acid do not irritate the unbroken skin but when ingested, may release free acid in the stomach causing local irritation.

Central nervous system:

(a) **Analgesia:** Aspirin, introduced as an analgesic-antipyretic in 1899, is still an important drug in the therapy of pain and inflammation. Salicylates, unlike the opioid analgesics, produce relief of pain without hypnosis or marked impairment of mental activity. They are mainly useful for relieving dull-aching, throbbing pain of low intensity coming from integumental structures

such as muscles and joints. They are also effective in relieving pain of dysmenorrhoea and toothache. They are not useful in shooting or visceral pain.

The salicylates alleviate pain probably by central as well as peripheral action. The thalamus, as mentioned previously, is responsible for the integration of pain sensation and also for the emotional reaction to pain. The salicylates are believed to act at the thalamic and hypothalamic sites.

In single doses, salicylates produce only analgesic action. With continued administration of larger doses, on the other hand, salicylates exert marked anti-inflammatory activity and relieve vascular congestion and edema. Human and animal experiments have shown that salicylates, when administered intraperitoneally, produce relief of pain evoked by intraperitoneal administration of bradykinin, while on intravenous administration, they are without any effect. Similar effects have been observed with other NSAID. In contrast to this, the opioid analgesics are ineffective peripherally. It appears, therefore, that although aspirin and allied drugs have central actions, they have important peripheral analgesic action, and it may be rational to combine aspirin with opioid analgesic like codeine for a synergistic effect. Aspirin inhibits the biosynthesis of P.G.s by irreversible acetylation and consequent inactivation of P.G. synthetase in contrast to newer NSAID which cause its reversible inhibition.

Salicylates probably do not affect the emotional reactions (anxiety, worry, fear) to pain and hence, a combination of salicylates with a hypnotic or a tranquillizer may be advantageous. Toxic doses of salicylates produce stimulation of the central nervous system followed by depression.

(b) *Antipyretic action* : In fever, the thermostatic mechanism is set at a higher level even though it is not completely deranged. Salicylates act centrally to reset this mechanism at the normal level and thereby bring down the temperature; in

a normal individual they do not show any demonstrable antipyretic activity.

The exact mechanism of the antipyretic action is not known. Salicylates, paracetamol and other antipyretics have been demonstrated to inhibit brain prostaglandin synthesis and release. Salicylates do not reduce heat production but increase dissipation of heat mainly by producing cutaneous vasodilatation and possibly but not necessarily by increased sweating. They do not affect the pathological process responsible for infection. Even though sweating assists the reduction of body temperature by salicylates, fever can be reduced even when sweating is blocked by prior administration of atropine.

(c) *Respiration* : Salicylates stimulate respiration as a result of direct and indirect actions.

As a result of their metabolic effect, therapeutic doses of salicylates increase the consumption of oxygen primarily by the skeletal muscles; this results in increased production of carbon dioxide. Increased carbon dioxide production leads to a direct stimulation of the respiratory centre producing an increase in the depth and to some extent in the rate of respiration.

With the entry of salicylates into the brain, the medullary respiratory centre is stimulated directly. In addition, salicylates also stimulate the chemoreceptors. This produces an increase in the rate as well as the depth of respiration leading to hyperventilation. The plasma carbon dioxide is washed out as a result of this hyperventilation, producing respiratory alkalosis. In man, a plasma level of 35 mg. per cent of salicylates is usually associated with hyperventilation and severe dyspnoea occurs when the level approaches 50 mg. per cent.

Acid-base balance and electrolytes: The respiratory alkalosis produced by therapeutic doses of salicylates is countered by excretion of alkaline urine containing bicarbonate along with sodium and potassium. This is termed the stage of *compensated respiratory alkalosis*. Reduction in the bicarbonate and potassium levels reduces the buffering capacity of the extracellular and the

intracellular fluids respectively and a patient on salicylate therapy is more prone to develop acid-base imbalance than a normal individual.

Hypokalemia as a result of urinary loss of potassium is accompanied by water loss through lungs due to hyperventilation, through skin via augmented sweating and through urine as a result of alkalosis. This may lead to dehydration and hypernatremia.

With toxic doses of salicylates hypokalemia is aggravated, the respiratory centre is depressed and metabolic acidosis develops. The mechanism of these effects is discussed later.

As a result of nephrotoxicity, aspirin and other NSAID can sometimes cause hyperkalemia (see later).

Gastrointestinal tract: The ingestion of salicylates may produce epigastric distress, nausea and vomiting. Nausea and vomiting with salicylates are induced both as a result of stimulation of the chemoreceptor trigger zone and irritation of the mucous membrane of the stomach. Dyspepsia occurs in approximately 5-10 per cent of patients taking salicylates. Salicylates can cause erosive gastritis, frank peptic ulceration and gastrointestinal haemorrhage, leading to hematemesis or melena.

The acid pH of the stomach favours the existence of salicylate in unionized form. The non-ionized form of salicylates is, however, relatively water insoluble; hence, it tends to adhere to the gastric mucosa thereby producing irritation. Further, local absorption into the mucous cell causes inhibition of PG synthesis, thus, causing a loss of the protective effect on the stomach. Salicylates also reduce the motility of the stomach and increase the gastric emptying time. These effects increase the period of contact of salicylate with the gastric mucosa.

To avoid gastric irritation, salicylates may be administered after food. Alkalies induce ionization of salicylates, thereby reducing their gastric absorption and local irritant effect. As the ionized salicylate is more water soluble, it tends to pass

more quickly into the intestine and does not adhere to the mucous membrane of the stomach. It is, therefore, customary to administer sodium bicarbonate along with salicylates. Administration of PGE analogue along with aspirin has been demonstrated to have a protective effect on the stomach mucosa.

Anti-inflammatory and anti-rheumatic effect : Salicylates suppress the clinical signs and improve the clinical picture in acute rheumatic fever and rheumatoid arthritis. Salicylates thus reduce only the 'inflammatory component' of the disease, leaving the 'tissue component' unaffected. Salicylates reduce the capillary permeability, thereby minimising the exudation of fluid and development of inflammatory edema. In addition to their action on P.G. synthesis, salicylates, in large doses, may affect other cellular and immunological processes in the mesenchymal and connective tissues.

Prostaglandins present in the inflammatory exudate are potent vasodilators and can cause edema, erythema and pain following intradermal injection. It has been suggested that aspirin-like drugs, by inhibiting the synthesis of prostaglandins, prevent sensitization of the pain receptors of chemicals such as histamin, 5HT and bradykinin, the known chemical mediators of pain and inflammation.

The kinins (e.g. bradykinin) are formed from kininogen by the action of kallikrein and can produce the cardinal signs of inflammation when this system is activated by a variety of stimuli. Aspirin is known to inhibit the formation of active kallikrein from inactive plasma and leucocytic kallikrein.

The acidic mucopolysaccharides such as hyaluronic acid and chondroitin and mucoitin sulfuric acid constitute the ground substances of the extracellular matrix. Salicylates and a wide variety of other anti-inflammatory agents including phenylbutazone, indomethacin and the corticosteroids inhibit the mucopolysaccharide biosynthesis. Such inhibition may reduce edema, tissue

swelling and inflammatory response.

Immunological phenomena : Salicylates suppress a variety of antigen-antibody reactions *in vivo* including systemic anaphylaxis induced by egg-white challenge in rabbits, allergic encephalomyelitis in guineapigs and serum sickness in man. They also prevent the release of histamine as a result of antigen-antibody reaction *in vitro*. Salicylates, however, do not interfere significantly with the development of agglutinins following typhoid inoculation in humans. It is claimed that the salicylates exert their beneficial effect in rheumatic fever by virtue of their action on the immunological phenomena. Further they may reduce the cell-mediated immunity.

Uricosuric effects : Urate present in the glomerular filtrate is reabsorbed by the proximal tubules of the kidney and the main excretion of urate in urine occurs due to its secretion by the distal tubule. Salicylates exert biphasic action on the excretion of urate. In small doses (1-2 g. per day), salicylates interfere with urate secretion by the distal tubule thereby elevating the plasma urate level. Large doses (over 5 g. per day) inhibit the reabsorption of urate by the proximal tubule, which can cause uricosuria. The high doses of salicylates required to produce uricosuria, however, usually result in adverse effects. Further, salicylates neutralize the action of other commonly used uricosuric agents like probenecid, sulfinpyrazone and phenylbutazone, if used in conjunction with them. Hence, they are not useful in the treatment of gout.

Cardiovascular system : Therapeutic doses of salicylates do not produce any deleterious effects on the cardiovascular system. In toxic doses, however, they produce a direct paralysis of the vasomotor centre.

Hepatic and renal effects : Salicylates in therapeutic doses do not modify hepatic and renal functions except for a transient increase in the urine cell count and occasional traces of albumin and/or tubular casts in urine. Salicylates increase

the secretion of bile by stimulation of the hepatic parenchyma (*choleretic action*) but reduce the total concentration of cholates in bile. In large doses, particularly in children, salicylates have been reported to cause abnormal liver function tests and even acute hepatic necrosis.

Blood: Salicylates do not affect the normal leucocyte count. However, they reduce the leucocytosis and lower the high erythrocyte sedimentation rate observed in acute rheumatic fever. The latter effect is probably due to a reduction in the plasma fibrinogen content as a result of antirheumatic activity of salicylates. Paradoxically, in some patients, salicylates may increase the plasma fibrinogen level and raise the sedimentation rate.

Aspirin has been shown to inhibit platelet aggregation. Platelets are known to play an important role in thrombus formation. The drug inhibits adenosine diphosphate (ADP) release from platelets. Further, aspirin inhibits the synthesis of prostaglandin endoperoxide, thromboxane A₂, which causes platelet aggregation. Among anti-inflammatory agents, aspirin is unique in that a single oral dose may have anti-platelet effect for 4 to 7 days. The use of aspirin in the prevention of thromboembolic disease is described elsewhere. (See Chapter 29). Non-acetylated salicylates such as sodium salicylate do not possess such anti-platelet action.

Endocrine effects : Salicylates, in large doses, stimulate the hypothalamic sympathetic centres and induce release of adrenaline from the adrenal medulla.

Salicylates interfere with the binding of thyroid hormones with their binding proteins, especially thyroxine binding albumin. This comes in the way of interpretation of serum thyroxine and tri-iodothyroxine values.

Metabolic effects : The uncoupling of oxidative phosphorylation by salicylates leads to conversion of a large part of energy derived from oxidation into heat. Large doses of salicylates may, thus, lead to hyperpyrexia, increased protein

catabolism leading to aminoaciduria and a negative nitrogen balance.

Large doses of salicylates produce hyperglycemia and glycosuria in normal individuals. In certain diabetic individuals, on the other hand, salicylates can reduce the blood sugar level and glycosuria. This effect is probably due to an enhanced peripheral utilization of glucose and inhibition of neoglucogenesis induced by salicylates.

Salicylates inhibit synthesis and enhance breakdown of tissue fatty acids. They also inhibit the release of free fatty acids from adipose tissue and reduce serum cholesterol levels in very high doses.

Absorption, fate and excretion : Salicylates are absorbed from the stomach and largely from the upper part of the small intestine. Sodium salicylate is absorbed more quickly than aspirin. On oral administration of a single therapeutic dose, appreciable plasma concentrations are found within 30 minutes, peak plasma level is achieved within 2 hours and approximately 50 per cent of the dose is eliminated in urine within 24 hours. The plasma half-life ranges from 2 to 8 hours. Factors such as particle size, pH of the gastrointestinal tract, solubility of the salicylate preparation and presence of food in the stomach modify the absorption.

Both salicylic acid and methyl salicylate are absorbed from intact skin, especially when applied in alcohol, petrolatum, lard or lanolin base and systemic poisoning in children has been reported following such local applications.

After absorption, approximately 50 to 80 per cent of the salicylate is bound to plasma proteins, mainly albumin. It is rapidly distributed through most of the tissues and achieves a significant concentration in the saliva, milk, spinal, synovial and peritoneal fluids and in the erythrocytes. High salicylate concentrations are observed in the liver, heart and muscle while the brain contains relatively smaller amounts.

Aspirin, even though absorbed as such, is subject to considerable first pass hepatic metabo-

lism (50-60%) to salicylate and is further hydrolysed in the blood and tissues to salicylic acid. The plasma levels of this drug in undissociated form are, therefore, low and of this, only a negligible portion is bound to plasma albumin.

Like phenytoin, salicylates exhibit dose dependent pharmacokinetics. At lower dose levels (300-600 mg individual doses), the plasma level of a salicylate increases in proportion to the dose. At higher dose levels (1-2 g individual doses), the increase in the plasma level is disproportionate and severe toxicity can occur.

Salicylates are mainly metabolized in the liver and excreted in urine in the form of conjugates with glycine and glucuronic acid. A small portion is oxidised to gentisic acid and excreted in the urine. Constant blood levels can be maintained by administering salicylates at 4 to 6 hourly intervals.

An alkaline urine, by ionizing the salicylate to a water soluble and indiffusible form, prevents salicylate back-diffusion in the distal tubule and enhances salicylate excretion. Thus, the concentration of free salicylate in urine varies considerably (10 per cent to 80 per cent) according to urinary pH. Salicylate excretion is reduced by probenecid, oliguria and kidney failure and is augmented by diuresis.

Adverse reactions:

(a) **Allergic reactions :** These are uncommon, occurring in about 1 in 500 patients. Salicylate intolerance may be manifested as skin rashes, urticaria, pruritus, angioneurotic edema, bronchial asthma, anaphylactic shock or thrombocytopenic purpura. Aspirin has been more commonly involved in the precipitation of bronchial asthma, particularly in persons with an allergic diathesis and this condition at times may prove refractory to therapy. Salicylate induced angioedema and anaphylaxis are amenable to adrenaline. Aspirin can induce idiosyncratic mild haemolysis in individuals with glucose-6-phosphate dehydrogenase deficiency. Salicylic acid and its derivatives are ingredients of a large number of substances including fruits like apples,

grapes, oranges, peaches and plums, soaps containing oil of wintergreen, perfumes, beverages (especially birch beer), tooth pastes, gum and lozenges. Individuals with idiosyncrasy to salicylates should be warned against taking proprietary drug mixtures, which often contain salicylates.

(b) **Gastrointestinal tract** : Salicylates sometimes cause dyspepsia, nausea, vomiting and heartburn. The present evidence indicates that there is little difference among various preparations. The ulcerogenic action of aspirin occurs less frequently when the drug is given in a buffered solubilized form. The actual blood loss in most cases is about 3-6 ml. per day in subjects taking 3-4 g. of aspirin daily. Occasionally, salicylates can cause haematemesis and prolonged therapy can lead to anemia. The incidence of major G.I. bleeding due to aspirin is estimated at 15 per 100,000 chronic aspirin users per year.

(c) **Haemopoietic system** : Salicylates in large doses reduce the plasma prothrombin level, by interfering with utilization of vitamin K in the liver. Salicylate induced hypoprothrombinemia can be reversed by administration of vitamin K. Salicylates exert a synergistic effect with the coumarin anticoagulants on prothrombin synthesis and hence, these drugs should be avoided by patients receiving oral anticoagulant drugs. For similar reasons, cautious use of salicylates is also indicated in individuals with hepatic damage and in those who are about to undergo surgery.

(d) **Reye's syndrome** : This serious and often fatal complication occurs a few days after a viral infection, especially influenza and varicella, in children between the ages of 6 months and 12 years. There occur anicteric liver dysfunction due to hepatic mitochondrial injury and a consequent metabolic encephalopathy. There is epidemiological evidence to associate administration of aspirin during the initial viral infection and the subsequent occurrence of this serious disease.

(e) **Pregnancy and infants** : Taken at term aspirin by inhibiting PG synthesis in the uterus may delay the onset of labour and may cause

greater blood loss at delivery. The administration of aspirin or indomethacin for therapeutic purposes at term has been reported to cause serious pulmonary hypertension in the newborn. Salicylates readily cross the placental barrier, and may prove toxic to the newborn as the ability of newborn to detoxify and excrete salicylates is poor. The toxic manifestations in newborn include hyperpnoea and haemorrhages. Hypoglycemia after prolonged salicylate therapy has been reported in infants. In addition, premature closure of patent-ductus arteriosus may occur.

(f) **Salicylism** : Prolonged administration of salicylates in the treatment of rheumatic fever or rheumatoid arthritis may produce a condition of mild salicylate intoxication termed salicylism. The syndrome usually develops when the plasma salicylate level exceeds 25 mg. per cent and is characterised by headache, dizziness, vertigo, tinnitus, difficulty in hearing and dimness of vision; drowsiness, lethargy and mental confusion, nausea, vomiting and diarrhoea may also occur. These symptoms may be associated with tachypnoea and respiratory alkalosis. The signs and symptoms of salicylism are reversible on cessation of therapy.

(g) **Acute salicylate intoxication** : Acute salicylate intoxication may be due to overzealous therapy in infants or an accidental ingestion by children and adults. A serum salicylate level of 50 mg% indicates mild toxicity; levels above 75 mg.% are potentially fatal. The characteristic features of acute salicylate intoxication are acid-base and electrolyte disturbances, hyperglycemia, dehydration, hyperpyrexia, gastrointestinal irritation and occasional haemorrhages. The disturbances of the central nervous system include restlessness, vertigo, tremor, apprehension, hallucinations, generalized convulsions and coma. Skin eruptions are usually not seen unless salicylate medication has been continued for more than a week. Moderate doses of salicylates, as discussed previously, produce compensated respiratory alkalosis. With higher doses, however, true metabolic acidosis supervenes because of following

factors :

(i) Salicylates in toxic doses depress the respiratory centre with the result that the enhanced carbon dioxide production as a result of their metabolic effect outstrips its pulmonary washout. Enhanced carbon dioxide production cannot be antagonized by body buffers such as bicarbonate as they are already exhausted during compensation for respiratory alkalosis. This leads to a decrease in the pH of the plasma and an increase in plasma carbon dioxide.

(ii) Salicylates which exist in the plasma mainly in the ionized form contribute considerably to a reduction in the plasma pH.

(iii) The depression of kidney function, secondary to vasomotor depression following toxic doses of salicylates, results in an accumulation of strong acids like sulfuric acid and phosphoric acid produced during metabolism.

(iv) Salicylate induced derangement of the carbohydrate metabolism leads to an accumulation of pyruvic, lactic and acetoacetic acids.

The picture of hyperpnoea, hyperglycemia, polyuria, dehydration and ketoacidosis seen with salicylate intoxication has to be differentiated from diabetic ketoacidosis. This is usually done by careful history taking and by the presence of C.N.S. stimulation and petechial haemorrhages observed with salicylate poisoning.

Treatment : Acute salicylate intoxication necessitates prompt hospitalization for treatment of dehydration, hyperthermia and acid base imbalance. Gastric lavage is performed to eliminate the unabsorbed drug from the stomach. Intravenous fluids are administered to correct dehydration; external cooling with cold water or alcohol is carried out to reduce the temperature. Vitamin K and blood transfusion are administered to prevent or treat the haemorrhagic complications and shock. Hypokalemia is corrected by administering potassium through the intravenous drip and ketosis is treated by intravenous dextrose. Metabolic acidosis is corrected by administration of sodium bicarbonate. Administration of sodium bicarbonate, however, carries with it the danger of metabolic alkalosis. It is, therefore, imperative

to measure blood pH as well as plasma bicarbonate levels before resorting to vigorous bicarbonate therapy as both plasma carbon dioxide and bicarbonate are reduced in the state of compensated respiratory alkalosis and administration of bicarbonate under such conditions would produce severe alkalosis and tetany.

Sedatives like barbiturates are dangerous when the patients show excitement with salicylate intoxication. These agents, by producing respiratory depression, may aggravate metabolic acidosis and produce coma.

Salicylate excretion can be enhanced by alkalinizing urine and by increasing the urinary output. This, however, has to be achieved by cautious administration of alkalis and fluids (0.9 per cent saline with 2 per cent dextrose and 2 per cent sodium bicarbonate at the rate of about 2 litres per hour) with frequent determinations of blood pH and plasma CO₂ to prevent metabolic alkalosis. Peritoneal dialysis with a solution containing albumin to bind the drug or haemodialysis are more sophisticated, efficient and safer methods to remove salicylates from the body. In very small children in whom haemodialysis is not suitable, exchange transfusion is recommended and gives good results.

Preparations and dosage :

(i) Acetyl salicylic acid I.P. (Aspirin). Dose : 0.3 to 0.6 g. by mouth for relief of integumental pain; in the treatment of acute rheumatism, 4 to 8 g. daily in divided doses.

(ii) Soluble aspirin tablet I.P. contains aspirin (300 mg.), citric acid (30 mg.) with calcium carbonate (100 mg) and saccharin sodium (3 mg.). When mixed with water, citric acid reacts with calcium carbonate to form calcium citrate solution and this dissolves aspirin forming calcium acetyl salicylate. It is not possible to dispense the latter directly in tablet form, as it is hygroscopic and is rapidly hydrolysed in the presence of moisture. Dose : same as above

(iii) Buffered aspirin tablets contain aspirin and an antacid like magnesium hydroxide, aluminium hydroxide or aluminum glycinate.

(iv) Sodium salicylate I.P. has a characteristic sweetish, saline, unpleasant taste and is soluble in water. It is usually administered in a mixture form with alkali. It is available commercially as 500 mg tablets (Succisalyl forte). Dose : for integumental pain 0.6 to 2 g., for acute rheumatic fever, 5 to 10 g. daily in divided doses.

(v) Methyl salicylate I.P. (oil of Wintergreen). It is employed only for topical application as a counter-irritant e.g. methyl salicylate liniment 25 per cent v/v in peanut oil, methyl salicylate ointment 50 per cent in white bees wax and hydrous wool fat.

(vi) Salicylic acid I.P.: Salicylic acid ointment I.P. contains 2 per cent salicylic acid w/w while Whitfield's ointment contains 6 per cent benzoic acid and 3 per cent salicylic acid.

Therapeutic uses of salicylates :

(a) **Local application** : Salicylic acid is used for its keratolytic, fungistatic and mild antiseptic activity (see Chapter 57).

(b) **As analgesic-antipyretic** : Salicylates are beneficial in a variety of conditions characterised by integumental pain. They are employed in arthralgias, myalgias, neuralgias, toothache, headache and dysmenorrhoea. For analgesia, salicylates are used either alone or in combination with an opioid analgesic like codeine. When combined with opioid analgesics, aspirin can reduce the dose of the former and fewer adverse effects of both drugs might result.

Aspirin and other PG inhibitors are valuable in primary dysmenorrhoea. Treatment is started on the first day of the menstrual period and is continued for 2-3 days.

In doses of 300-1200 mg, aspirin shows graded responses. Doses higher than 1200 mg. however, simply increase the risk of toxicity and should not ordinarily be prescribed.

They are also useful in similar doses in the symptomatic treatment of fever. Because of their proposed association with Reye's syndrome, salicylates should not be prescribed to children with viral fevers.

(c) **Anti-inflammatory** : Aspirin is commonly

used to treat inflammatory conditions such as arthritis and fibromyositis. It can modify or diminish but does not arrest the inflammatory response.

(d) **As antirheumatic** : Salicylates when administered in a sufficiently large dose, produce within 24 to 48 hours dramatic relief of the signs and symptoms of inflammation. There is considerable and often complete relief of pain, and a significant reduction in swelling, immobility, heat and redness of the joints involved. The fever is reduced, the pulse rate slows down and further joint involvement is prevented. Salicylates, however, cannot prevent or reverse the cardiac complications, chorea, subcutaneous nodules or encephalopathy and fail to shorten the duration of the disease.

In S.L.E. aspirin may ameliorate arthritis and serositis but the vasculitic component caused by immune complex deposition is not much affected.

Aspirin, being a better analgesic, is preferred to sodium salicylate. The adult dose is 4 to 8 g. daily given at intervals, in 1 g. dose. For children the recommended daily dose is 120 mg. per kg. of body weight per day (with a maximum of 8 gm.) given in 4-6 divided doses. A plasma salicylate level of 25 to 40 mg. per cent usually achieves adequate control. Adverse effects like nausea, tinnitus and vomiting usually subside after continuation of therapy for 3 to 4 days. Full doses are continued for at least 2 weeks after disappearance of symptoms and signs of inflammation, and the drug is then gradually discontinued over a period of 7 to 10 days. Sudden salicylate discontinuation is likely to produce a relapse. Large doses of salicylates in patients with rheumatic carditis may increase the plasma volume, cardiac output and metabolic rate and this may occasionally precipitate congestive cardiac failure.

Glucocorticoids are useful in cases not responding to salicylates and appear to be more effective in the severely ill patients with high fever, rheumatic pericarditis and concomitant congestive cardiac failure or cardiac arrhythmias. Like salicylates, however, these agents do not affect the 'tissue component' of the inflammatory

process and the high doses in which they are administered may precipitate a variety of adverse reactions. The incidence of relapse after stoppage of corticosteroid therapy is relatively high. Some authorities recommend the use of salicylates and steroids together.

Concurrent penicillin therapy is recommended. This is discussed in Chapter 42.

For use of aspirin in rheumatoid arthritis, see Chapter 66.

(e) **As antiplatelet agent** : Aspirin has been used to prevent the formation of a platelet-fibrin thrombus. (See Chapter 29).

(f) P.G.s have been implicated in the maintenance of patency of ductus arteriosus. Aspirin and indomethacin have been used in this condition with some success. The treatment of Bartter syndrome (a rare condition associated with hypokalemia and increased plasma renin and aldosterone levels) with aspirin has been quite successful.

(g) **Miscellaneous** : Prophylactic doses of aspirin (600-900 mg.), indomethacin or ibuprofen have been shown to prevent symptoms of food intolerance in patients who showed acute G.I. symptoms after eating specific foodstuffs. Aspirin has also been shown to exert the beneficial effect in radiation induced and other diarrhoeas. These symptoms are probably mediated through prostaglandin release. Taken orally and applied locally, aspirin and other P.G. inhibitors have been found useful in reducing erythema due to sunburn in man.

Salicylate congeners : Salicylamide, a salicylate congener, is rapidly absorbed from the gastrointestinal tract and is eliminated equally rapidly by the kidney, predominantly as a glucuronide. The drug is not hydrolysed to salicylic acid in the body. Salicylamide is administered in the dose of 2 g., three to six times daily in the treatment of rheumatic fever and rheumatoid arthritis. The rapid urinary elimination of this drug makes the maintenance of a therapeutic plasma level difficult.

Diffunisal is a non-acetylated difluorinated

salicylate which has analgesic and antiinflammatory properties. There is some evidence to suggest that it has greater potency, better tolerance and a longer duration of action than aspirin.

II. PARA-AMINOPHENOL DERIVATIVES

The commonly used drug is paracetamol. The drugs acetanilid and phenacetin are no longer used in therapeutics.

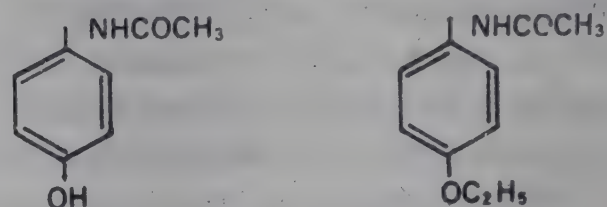


Fig 9.2 Paracetamol

Phenacetin

PARACETAMOL: This compound exerts analgesic and antipyretic effects like salicylates. Paracetamol is a potent antipyretic and is equi-analgesic with aspirin in therapeutic doses but devoid of significant anti-inflammatory effect. This could be due to its weak activity on peripheral prostaglandin synthetase; however, it equals the blocking effect of aspirin on this enzyme in the brain.

Unlike salicylates, this drug does not produce acid-base imbalance, electrolyte disturbances, gastrointestinal irritation nor does it affect blood clotting.

Absorption, fate and excretion : Paracetamol is rapidly absorbed on oral administration. Peak plasma levels are reached within 1/2 to 1 hour. Paracetamol is mainly excreted in urine as conjugation products of glucuronic and sulfuric acids. The ability of infant liver for glucuronidation of paracetamol is poor and this may result in enhanced toxicity of the drug in neonates.

Adverse reactions : (i) Paracetamol may cause fever, neutropenia, thrombocytopenia and skin reactions.

(ii) Paracetamol may occasionally produce anemia as a result of haemolysis. Individuals with

glucose-6-phosphate dehydrogenase deficiency may exhibit increased sensitivity to this drug.

(iii) Methemoglobinaemia occurs uncommonly with paracetamol.

(iv) Large doses of paracetamol produce extensive damage to the liver and may cause death due to liver failure. In fact, this is a major problem in acute paracetamol poisoning. The liver toxicity is probably due to the toxic metabolite *n*-hydroxy-*n*-acetyl-*p*-hydroxyaniline. Depletion of glutathione potentiates this hepatic toxicity whereas treatment with sulphydryl compounds such as cysteamine, *l*-methionine and *n*-acetyl cysteine is beneficial. *N*-acetyl cysteine may be administered orally as 5% solution in the dose of 140 mg/kg, followed by 70 mg/kg every 4 hours for 3 days.

Preparation and dosage : Paracetamol is used as a substitute to aspirin as an analgesic and antipyretic. Dose: 300 to 600 mg. in tablet or powder. The total daily dose should not exceed 2.5 g. in adults. It can be used in a liquid dosage form in children.

III. PYRAZOLONE DERIVATIVES

These are

- Aminopyrine and antipyrine
- Phenylbutazone and oxyphenbutazone
- Other drugs like phenyldimethyl pyrazolone (analgin, dipyrone).

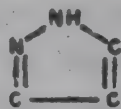


Fig. 9.3 : Pyrazolone ring

AMINOPYRINE AND ANTIPYRINE are both very potent analgesic and antipyretic agents and possess significant anti-inflammatory activity. Aminopyrine is a more potent anti-inflammatory agent than antipyrine.

Both aminopyrine and antipyrine are completely and rapidly absorbed from the gut and are almost completely metabolised in the body. Aminopyrine is metabolized more rapidly than

antipyrine.

The therapeutic use of these compounds has declined considerably owing to their toxicity. The oral dose of the compounds is 300 to 600 mg. repeated at 4 hourly intervals.

PHENYLBUTAZONE : This compound initially used as a solvent for aminopyrine injection, is a potent anti-inflammatory drug.

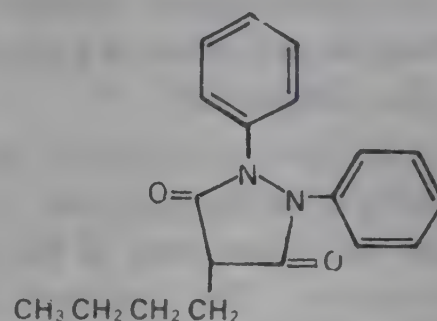


Fig. 9.4 : Phenylbutazone

Pharmacological actions : The anti-inflammatory activity of phenylbutazone exceeds that of salicylates, antipyrine and aminopyrine. The analgesic and antipyretic activity of phenylbutazone is, however, much less than that of salicylates. It also diminishes the reabsorption of urate by proximal renal tubules and exerts a uricosuric effect. Like salicylates, it inhibits the biosynthesis of prostaglandins.

Absorption, fate and excretion : The absorption of phenylbutazone on oral administration is rapid and complete, but on intramuscular administration, the drug remains localised at the site of injection for a much longer time. Phenylbutazone is extensively bound to plasma proteins (approximately 98 per cent). Increasing the dose of the drug results in an increase in the free, rapidly metabolizable form of this drug and hence fails to influence the plasma concentration of the drug significantly. Phenylbutazone is almost completely metabolized by the liver. A metabolite of the drug, oxyphenbutazone, shares anti-inflammatory and sodium retaining properties with phenylbutazone. Chronic phenylbutazone administration results in the stimulation of

the liver microsomal enzyme systems producing a faster detoxification of phenylbutazone itself and of other compounds like barbiturates.

Adverse reactions : It is poorly tolerated by many patients and produces a variety of adverse effects. Dyspepsia, epigastric discomfort, nausea and vomiting may occur in a large proportion of cases and the drug may have to be discontinued. Skin rashes, insomnia, euphoria, blurring of vision, optic neuritis, retinal hemorrhages, pancreatitis, vertigo, hematuria and convulsions have been reported. The serious adverse effects are as follows:

(a) Phenylbutazone may produce peptic ulcer and bleeding from an already existing peptic ulcer.

(b) The drug may produce serious hematologic reaction such as megaloblastic anemia, aplastic anemia, agranulocytosis and thrombocytopenic purpura. Hepatitis, nephritis and exfoliative dermatitis as manifestations of phenylbutazone intolerance have been reported. The drug may produce jaundice and its combination with aminopyrine has resulted in many cases of azotemia with or without anuria.

(c) Edema as a result of sodium and water retention may develop during phenylbutazone therapy. This may precipitate congestive cardiac failure or pulmonary edema in patients with impaired cardiac function.

(d) Phenylbutazone may reduce the iodine uptake by thyroid, occasionally producing hypothyroidism and myxoedema. Because of its high protein-binding, it displaces oral anticoagulants, oral hypoglycemics and sulfonamides from the plasma protein binding sites. This can lead to increased pharmacological toxicity of the displaced drug.

(e) A relationship between treatment with phenylbutazone and subsequent leukaemia has been suggested but not proven.

Preparations and dosage :

(i) Phenylbutazone tablet N.F. contains 100 mg. of the drug in an enteric coated tablet. Dose:

200 to 400 mg. daily in divided doses.

(ii) Injection phenylbutazone sodium is available in ampoules containing 200 mg. of the sodium salt per ml. Administered in the buttock by deep intramuscular injection, it may occasionally produce damage to the sciatic nerve. Dose : 200 to 600 mg.

Therapeutic uses:

(a) **Gout :** In the dose of 600 mg. daily, phenylbutazone produces satisfactory relief from pain and joint immobility in acute gout. (See Chapter 66).

(b) **Ankylosing spondylitis :** The drug produces improvement in 50 to 70 per cent of the individuals. The patients can be maintained subsequently on 100 to 200 mg. of the drug per day.

(c) **Rheumatoid arthritis and osteoarthritis :** (See Chapter 66.)

Because of its toxicity and availability of better drugs, phenylbutazone is now rarely recommended.

OXYPHENBUTAZONE (Tanderil, Suganril, Oxyrin): This compound, a metabolic degradation product of phenylbutazone, is claimed to cause less gastric irritation than phenylbutazone. The drug, however, shares all the toxic effects of phenylbutazone and does not seem to have any significant advantage over phenylbutazone.

ANALGIN (Novalgin): It has potent analgesic and antipyretic actions but no uricosuric effect. It does not offer any distinct advantage over aspirin except that it can be injected. The toxic effects are similar to those of phenylbutazone, and include blood dyscrasias. Hence, it is risky and unjustifiable to use this drug routinely, simply to relieve pain and fever where aspirin or paracetamol would be adequate.

IV. INDOLE ACETIC ACID DERIVATIVES

INDOMETHACIN (Indocid): This indole acetic acid derivative is a potent anti-inflamma-

tory agent.

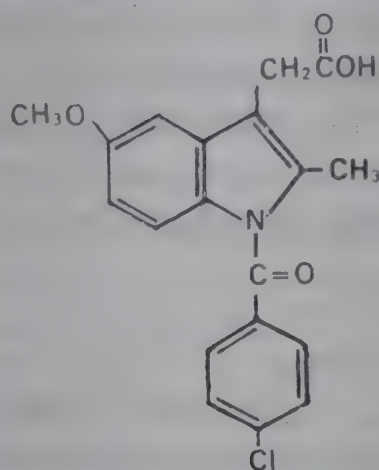


Fig. 9.5: Indomethacin

Pharmacological actions: It has anti-inflammatory, analgesic and anti-pyretic actions. In patients with rheumatoid arthritis with swollen joints, it brings about a quick reduction in the joint swellings. However, the weight of evidence indicates that the drug is not superior to the other established drugs like aspirin for this purpose.

Indomethacin is particularly useful in the treatment of acute attacks of gout, where it relieves pain within 2 hours of the first dose. It also acts as an analgesic even in the absence of obvious inflammation e.g. osteoarthritis, ankylosing spondylitis.

It inhibits prostaglandin synthesis. In addition, it has been shown to inhibit phosphodiesterase, thus increasing the intracellular concentration of cyclic AMP. It interferes with the migration of leucocytes into the inflammatory sites.

Absorption, fate and excretion : There are great species differences in absorption, distribution and metabolism of the drug. In man, given orally, it is almost completely absorbed, reaching a peak plasma concentration within 1 1/2 to 2 hours, is mainly metabolised by the liver, and is rapidly eliminated by the kidneys as glucuronide. Nearly 50-90 per cent of a single dose is excreted in urine within 24 hours. Its action is more prolonged than is suggested by its $t_{1/2}$ (2 hours) though it is shorter than that of phenylbutazone.

Adverse reactions : The reported incidence of adverse effects has ranged from 25 to 50 per cent.

Even with the low doses, the incidence is 15-20 per cent. Headache is the most common effect, followed by giddiness, mental confusion, blurring of vision, depression and psychotic disturbances. - Some of these effects would make it dangerous for the patient to drive a vehicle. Less common adverse effects are nausea, vomiting, dyspepsia, diarrhoea, skin rashes and rarely blood dyscrasias. Peptic ulceration associated with bleeding and liver damage have also been reported. The drug may mask symptoms and signs of infection. It can cause reduction in renal clearance of lithium and thus, a rise in serum lithium level in patients on lithium therapy. It may cause sodium retention and transient rise in blood urea and blood creatinine.

Preparation and dosage: Indomethacin 25 mg. capsules. Total daily dose recommended is 50-150 mg. in divided doses, after food. Indomethacin suppository is also available.

Therapeutic uses: Although the drug is effective in rheumatic disorders, it cannot be recommended as the drug of choice because of its toxicity. It may be preferred in the treatment of acute gouty attacks and in ankylosing spondylitis. It does not interfere with the uricosuric effect of probenecid. Its other uses are similar to those of phenylbutazone.

SULINDAC is a fluorinated derivative of indomethacin. It has longer duration of action and is given orally in the dose of 100-200 mg. twice a day.

TOLMETIN: This new drug, a pyrrole acetic acid derivative, resembles indomethacin in its actions and its toxicity. It is, however, less potent than indomethacin.

V. PHENYLACETIC ACID DERIVATIVES

Diclofenac sodium (Voveran, Voltarin) : This new NSAID has properties and limitations similar to those of other NSAID. It can be admini-

stered orally and intramuscularly.

A large scale study confirms that dipyrrone (analgin) is a major cause of agranulocytosis and that phenylbutazone, diclofenac and indomethacin can cause aplastic anemia. They should be used only when aspirin and other NSAID are ineffective.

VI. PROPIONIC ACID DERIVATIVES

These compounds like ibuprofen, naproxen,

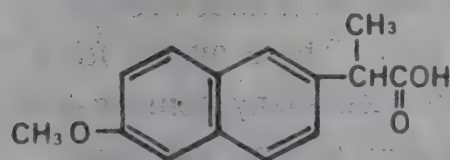
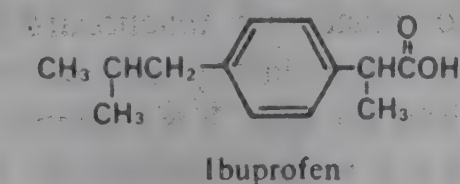


Fig. 9.6: Naproxen

fenoprofen, flurbiprofen and ketoprofen have analgesic-antipyretic and anti-inflammatory properties similar to aspirin but are better tolerated orally and the incidence of adverse reactions is low. They can, however, cause most of the adverse reactions produced by aspirin, including gastric irritation and ulceration. Further, any patient who is allergic to aspirin may also suffer a severe reaction following administration of any of these drugs. These drugs are highly bound to plasma albumin (92-99%) and, like aspirin, can displace drugs such as hydantoins, sulfonylureas and warfarin. They, however, differ in their pharmacokinetics and hence, the duration of action following single doses. They are particularly useful in patients with rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, who cannot tolerate aspirin. Of these agents, naproxen has long plasma half life and can be administered twice a day. They are at present much more ex-

pensive than aspirin. Some of the propionic acid derivatives in use at present are given in Table 9.1

Table 9.1: Propionic acid derivatives

Name	Plasma half life (h)	Oral dose
Ibuprofen	2	0.4 - 0.6 g. t.i.d.
Fenoprofen	2.5 - 3	0.3 - 0.6 g. t.i.d.
Ketoprofen	1.6 - 1.9	0.05 g. t.i.d.
Flurbiprofen	2.5 - 6	0.05 g. t.i.d.
Naproxen	12 - 15	0.25 g. b.i.d.
Pirofen		0.4 - 0.6 g. b.i.d.

NABUMETONE (Relifex): This new NSAID is a prodrug. Being non-acidic and non-active, it is claimed not to cause stomach ulceration. After absorption, it is rapidly metabolised to form an active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) which is a potent PG-synthesis inhibitor. It is effective in once daily dosage. It is under evaluation

VII. FENAMATES

MEFENAMIC ACID (Pontstan): This is an anthranilic acid derivative useful in chronic and dull aching pains. However, it is a weaker analgesic than aspirin. Toxic reactions include gastric upset, diarrhoea, dizziness, headache, skin rashes, hemolytic anemia and blood dyscrasias.

Flufenamic acid has similar properties.

ENFENAMIC ACID (Tromaril): This is an anthranilic acid derivative, N-phenylethyl anthranilic acid. Present evidence indicates that it has analgesic, antipyretic and anti-inflammatory properties. It is used orally in the dose of 1200-2400 mg. per day, in three divided doses. It can cause gastro-intestinal adverse effects.

VIII. OXICAMS

PIROXICAM (Feldene): This NSAID is

structurally different from other agents. Given orally, it is well absorbed and has a long half life of 38-45 hours. Hence, it can be administered once a day. Doses between 10 and 20 mg produce analgesic-antipyretic effect whereas larger doses (20-40 mg) are needed for the anti-inflammatory effect. Like aspirin it does cause gastric irritation and other G.I. disturbances. It has been used to treat rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and acute gout.

PHARMACOTHERAPY OF PAIN

The boundaries between normal discomfort and pathologic pain are often obscure. The intensity of pain suffered differs enormously with the personality, intelligence and culture of the individual. Tribal people often display a stoic disregard for pain. As a generalisation, pain is complained of more vehemently by people belonging to the more affluent and the elite sections of the population.

Emotional stress and anxiety adversely affect the pain response, while other factors which enhance its severity are debility and fatigue. Pain often becomes worse during the night when the distractions of every day life are absent and the patient has time to ruminate his ailment. Protracted severe pain can become so dominant a factor in a patient's life that it can eventually lead to both physical and psychological exhaustion.

The relief of pain by the use of appropriate drugs forms an important aspect of therapeutic skills in practice. The choice of treatment would depend upon:

- (1) the nature of the painful disease,
- (2) the mechanism by which it produces pain,
- (3) other associated complications and conditions, and
- (4) the risk of toxicity involved due to the drug so selected.

An attempt should always be made to find out the probable cause. *Where the cause is obvious,*

therapy should be directed to treat it. Thus, pain due to an abscess can be relieved by appropriate chemotherapy and surgery.

In patients in whom, for some reason, the cause cannot be treated, immediate relief of pain can be obtained by *treating the mechanism by which pain is produced* e.g. use of nitrites in angina pectoris, miotics in glaucoma and muscle relaxants in certain musculoskeletal disorders. Mechanism of production of abdominal pain is many times obscure and a demonstrable cause is absent in many cases. The pain in chronic duodenal ulcer can be relieved promptly by sodium bicarbonate powder. Individuals with "functional dyspepsia", are known to be benefited by 'carminatives' which have been used for ages. It is a common experience that a few seeds of cardamom, fennel or ginger can make the stomach comfortable after a sumptuous meal. These agents form the traditional ingredients of many stomach-ache powders and gripe waters sold in the market. Genuine intestinal or biliary colic, however, needs administration of an anticholinergic drug like belladonna or its active principle atropine.

In inflammatory conditions such as rheumatoid arthritis and gout, *the NSAID* can relieve pain without affecting the basic disorder. Some of the newer drugs used in rheumatoid arthritis are believed to induce remission. Some drugs such as colchicine may be relatively specific in that they may act in a single, inflammatory, painful condition viz. acute gouty arthritis.

Opioid and non-opioid analgesics are the most commonly employed agents *for symptomatic relief of pain*, without affecting any other aspect of the clinical condition. It is important to administer analgesics at the very onset of pain. The longer the pain is allowed to continue untreated, the less effective the analgesics become. This is seen especially in such conditions as migraine. *Severe pain of sudden onset* can produce shock and even death. In such cases, morphine group of drugs are indispensable and should not be with-

held simply for fear of initiating drug dependence e.g. in acute myocardial infarction, fractures and pneumothorax. These drugs, besides alleviating the severest pain, also induce a state of tranquillity, thus creating an indifference towards residual discomfort. When used with skill and discrimination, the adverse effects are not much bothersome. In order to give the maximum benefit to the patient these drugs should be administered in full doses, if necessary intravenously. It should be noted that patients with severe pain are remarkably tolerant to full therapeutic doses of morphine. If morphine is to be administered intravenously, it should be injected slowly, the dose being 2.5-5 mg. injected over 5 minutes. Pethidine has a shorter duration of action than morphine; this can lead to unsuspected undertreatment. Conditions in which morphine or pethidine is recommended here and the frequency of doses suggested make the possibility of drug addiction very remote. However, patients with acute pain treated with opioids for more than 5 - 7 days are likely to develop tolerance to the analgesic effects, so that if they need relief from pain after additional surgery, the usual doses will not give relief. Buprenorphine in the oral or sublingual dose of 0.3 to 0.6 mg. every 6 - 8 hours is an effective analgesic in *postoperative pain*.

Chronic cancer pain is often due to direct tumour involvement such as bone metastases, nerve compression or infiltration, and hollow viscus involvement. Such pain can be severe, unremitting, not responding to analgesics and demoralizing; it needs urgent relief. Drugs used in treating pain due to cancer include not only NSAID and opioids but also phenothiazines and antidepressants. Low doses of amitriptyline (25-75 mg/day) produce an analgesic effect independent of any antidepressant effect. Mild to moderate pain may respond to NSAID; they do not cause tolerance or physical dependence; they are particularly useful in pain due to bone metastases. Chronic use of opioids causes not only tolerance

but also physical dependence; however, psychological dependence is rare. For effective therapy, adequate, and increasing doses of opioids are needed; dependence is the rule but one should not worry about it. The opioids should be given on a regular basis to prevent pain rather than give them when the patient has to demand a further dose. Tolerance develops faster when the patient cycles between pain and analgesia than when analgesia is maintained continuously. The oral route is always preferable and oral morphine is perhaps the most commonly used opioid, followed by methadone. Buprenorphine can be used sublingually.

Equianalgesic doses of opioids are as follows: morphine I.M. 10 mg, oral 60 mg; pethidine I.M. 75 mg, oral 300 mg; methadone I.M. 10 mg, oral 20 mg; codeine oral 120 mg; pentazocine I.M. 60 mg, oral 180 mg; buprenorphine I.M. 0.4 mg, sublingual 0.8 mg. An equianalgesic dose is a recommended starting dose; the optimum dose for each patient is determined by titration. When given orally for mild to moderate pain, the following are equipotent with 650 mg of aspirin: codeine 30 - 60 mg, pethidine 50 mg, pentazocine 30 mg and propoxyphene 65 - 130 mg. However, for the treatment of severe pain, morphine is not only more potent but also more efficacious than aspirin.

For the symptomatic relief of *dull aching and chronic type of pain*, non-opioid, non-addicting analgesics like salicylates are preferred, and aspirin deserves the widespread popularity it enjoys for this purpose. The frequency of adverse effects due to this drug appears to be relatively low when one considers the annual world consumption of aspirin which now runs into several thousands of tons. The aspirin induced irritation of the stomach can be minimised by taking 200-300 ml of warm water along with it. Aspirin is effective in many kinds of pain, not merely those related to the musculo-skeletal disorders. It is also anti-inflammatory and anti-pyretic. It can be used over a prolonged period without fear of addiction.

Aspirin or newer NSAID are also useful in moderate *post-operative and post-partum pain and pain associated with injury to soft tissues*. The newer NSAID though perhaps better tolerated, are almost 10-20 times more expensive than aspirin. Phenylbutazone, indomethacin and related compounds are more toxic than aspirin and hence their routine use as substitutes for aspirin is not justified. Clinically, aspirin and paracetamol are equally effective as antipyretics and superior to tepid sponging. The combination of aspirin with codeine is synergistic as these drugs alleviate pain by different mechanisms.

The cause of *headache* is many times obscure in practice. Specific types of headache like migraine are treated by tablets of ergotamine and caffeine. Many headaches are, however, caused by anxiety, tension, fatigue or depression and use of proper psychotherapeutic drugs like diazepam or imipramine can give dramatic results. Realisation of this psychic aspect of pain will prevent other unnecessary therapy including extensive and irrelevant sinus operations. In such cases some minor adjustments in patient's life can be more therapeutic than even drugs. Headaches due to common cold, influenza or other fevers respond to administration of aspirin. Headaches due to sinusitis and eyestrain need specific treatment.

Backache presents similar diagnostic problems as headache. It can be due to many causes. Mental depression and nervous tension can many times produce backache. Failure to recognise this in women may lead to unnecessary correction of normal retroverted uterus or even its removal for no sensible reason.

It must be realised that pain can many times exist without the presence of any organic disease. In many patients it can be relieved without using any active drug. The phenomenon of pain is highly subjective and is associated with a *psychic reaction* involving fear, anxiety, apprehension and distress. In such circumstances, judicious use

of tranquillizers, antidepressants and placebos may produce beneficial effects and analgesics like aspirin can sometimes be combined with these drugs for effective therapy of pain.

Counterirritants applied as liniments can occasionally relieve dull-aching, localised musculoskeletal pain. Many times these drugs act as placebos. Their popularity is never on decline, whether one recommends them or not! However, even though they may not do any good at least they will do less harm and will not mask the diagnosis of the underlying disease.

The drugs used in the treatment of rheumatoid arthritis and gout are discussed in Chapter 66.

NSAID and renal damage : The relation between analgesic use and renal damage has now been confirmed. Phenacetin was the first drug proven to cause 'analgesic nephropathy'. But, all NSAID can cause acute or chronic renal damage following repeated use, sometimes as short as two weeks. Drugs with a long half life (naproxen and piroxicam) are more likely to cause renal damage than those with shorter half life (ibuprofen). Clinically, the renal injury can present itself in several forms: acute renal failure; mild asymptomatic renal impairment; chronic renal impairment due to papillary necrosis or interstitial fibrosis; and serious hyperkalemia. The first three are related to the action of NSAID to inhibit intrarenal PG synthesis; locally produced PGE₂ acts as an intra-renal vasodilator to counteract the vaso-constricting effect of angiotensin II and noradrenaline (as in shock). Inhibition of synthesis of PGs within the kidney has several effects: the protective intrarenal vasodilator effect is lost; renal blood flow and GFR are reduced (in people with pre-existing renal impairment); the natriuretic effect of PGE₂ on the renal medulla is lost with consequent sodium retention. The fourth effect (hyperkalemia) is due to diminished aldosterone synthesis secondary to inhibition of renin synthesis by NSAID. Hyperkalemia is particu-

larly likely to occur in patients with diabetes mellitus, renal disease and in those on potassium sparing diuretics. The risk of developing renal damage due to NSAID is increased by the concurrent presence of: old age; congestive heart failure; cirrhosis of liver; diabetic nephropathy; gout; renal or renovascular disease; and salt/volume depletion. Finally, NSAID enhance the effects of

vasopressin on the kidneys and can diminish excretion of free water.

Recent studies indicate that aspirin is perhaps safer in that its chronic use is less associated with analgesic nephropathy.

The possibility of chronic ingestion of analgesics should always be borne in mind while dealing with unexplained chronic renal damage.

10 Central Nervous System Stimulants

As compared to CNS depressants, the stimulants of the central nervous system are therapeutically not so useful as they lack selectivity of action. Further, excessive stimulation of CNS is followed by its depression. Some of the central nervous system stimulants are mainly used as *analeptics*. Analepsis is a Greek word which can be loosely translated as 'picking up those who have been cast down'. Analeptics stimulate the central nervous system and, in large doses, they cause generalised convulsions. Thus, these drugs have a wide range of effects of which, stimulation of breathing is only one, and perhaps may not be the dominant one.

Classification : The central nervous system stimulants can be classified as :

I. Those acting directly on the central nervous system.

(A) Predominantly cortical stimulants like xanthine alkaloids, amphetamine, methylamphetamine, methylphenidate and pipradrol.

(B) Predominantly medullary stimulants e.g. picrotoxin, pentylenetetrazol, nikethamide, amiphenazole, camphor and carbon dioxide.

(C) Predominantly spinal stimulants e.g. strychnine.

II. Those which stimulate the central nervous system reflexly e.g. lobeline, ammonia, veratrum and nicotine.

It should be remembered that the classification given above is arbitrary and a CNS stimulant, when administered in a sufficiently large dose, is capable of stimulating the entire central nervous system.

(A) STIMULANTS OF THE CEREBRAL CORTEX

XANTHINE ALKALOIDS : The three naturally occurring xanthine alkaloids caffeine, theophylline and theobromine are purine bases which occur in several plants all over the world. These alkaloids leave behind a yellow residue when heated with nitric acid and hence, the term xanthine derived from the Greek word 'xanthos' meaning yellow. Coffee prepared by grinding the seeds of *Coffea arabica* contains caffeine, tea from leaves of *Thea sinensis* contains caffeine and theophylline, while cocoa obtained by grinding seeds of *Theobroma cacao* contains caffeine and theobromine. The cola flavoured soft drinks also contain caffeine.

Pharmacological actions :

Central nervous system : Of the three xanthine alkaloids, caffeine possesses the most significant action on central nervous system, followed by theophylline and theobromine. Threshold doses of caffeine mainly act on the cerebral cortex, whereas larger amounts stimulate the medullary centres and toxic doses result in convulsions as a result of stimulation of the entire neuraxis including the spinal cord.

(a) *Cerebral cortex:* Caffeine in small doses produces a more rapid and clearer flow of thoughts, increases mental alertness, delays fatigue and drowsiness, and thus assists an individual towards greater sustained intellectual effort and association of thoughts and ideas. Caffeine also reduces reaction time, improves motor activity and augments conditioned reflexes. The cor-

tical effects may be produced by ingestion of 1 or 2 cups of coffee, one cup containing about 150 mg. of caffeine. Larger doses of caffeine (exceeding 300 to 500 mg.) produce irritability, nervousness, confusion of thought, insomnia, headache and tremors. Recently acquired motor skills calling for delicate muscular coordination and accurate timing may be affected adversely as a result of nervousness and tremors. Very large doses may cause focal and generalised convulsions, and theophylline is more potent than caffeine in this respect.

(b) *Medulla* : Larger doses of caffeine stimulate the respiratory, vasomotor and vagal centres. Caffeine induced respiratory stimulation is more marked in individuals breathing 3 to 5 per cent carbon dioxide than in normal individuals; this suggests that the drug probably increases the sensitivity of the respiratory centre to carbon dioxide. The stimulation of vasomotor and vagal centres tends to raise the blood pressure and induces bradycardia, respectively.

(c) *Spinal Cord* : Very large doses of caffeine produce an increase in reflex excitability of the spinal cord, and may lead to clonic convulsions and death in animals. In man no fatalities after caffeine ingestion or administration have been reported.

Cardiovascular system : Theophylline has the most prominent action on the cardiovascular system.

(a) *Heart* : Xanthines have a direct stimulant action on the myocardium and tend to increase the heart rate, the force of contraction and the myocardial oxygen consumption. The positive chronotropic action on the myocardium is antagonized by central vagal stimulation, particularly with caffeine, and therapeutic doses of caffeine may produce a variable effect on the heart rate. Large doses of caffeine, however usually produce palpitation, tachycardia and occasionally cardiac arrhythmias.

Increase in cardiac output with xanthines may occur even in the absence of tachycardia. The increased force of contraction assures a better

emptying of the heart and reduces the central venous pressure. In healthy individuals, the lowering of the venous pressure may outlast the cardiac stimulant effect; resulting in a fall in the cardiac output following an initial rise, but in individuals with congestive cardiac failure, the lowered venous pressure produces an increase in the cardiac output by achieving better emptying of the heart.

(b) *Blood vessels* : Xanthines tend to produce peripheral vasodilatation by a direct action on vascular smooth muscle and cause a decrease in cardiac preload.

(i) *Coronaries* : The coronary blood vessels are dilated and the coronary blood flow is increased.

(ii) *Cerebral blood vessels* : Xanthines produce a marked increase in the cerebral vascular resistance and reduce the cerebral blood flow and the cerebrospinal fluid pressure. It is this constriction that is believed to be responsible for the relief of hypertensive headache.

(iii) *Pulmonary blood vessels* : Xanthines produce relaxation of the pulmonary arterioles and reduce the pulmonary artery pressure. This effect is enhanced by the fall in central venous pressure.

(iv) *Blood pressure* : The direct cardiac stimulant action of xanthines tends to raise the blood pressure. This action is aided by the stimulant action of the vasomotor centre and is antagonized by the central vagal stimulation and peripheral vasodilator effect. Further, ingestion of caffeine is known to cause increase in plasma adrenaline and noradrenaline levels. Changes in blood pressure are, therefore, somewhat unpredictable. The combination of peripheral vasodilatation and increased cardiac output, however, raises the pulse pressure and the velocity of blood flow and thus tends to improve circulation. Large intravenous doses of xanthines produce a fall in blood pressure.

Smooth muscle : Xanthines also relax other smooth muscles, theophylline being more potent than caffeine or theobromine.

The most important therapeutic action of xan-

thines is on the bronchial smooth muscle which is promptly relaxed. Theophylline is able to abolish bronchospasm produced by histamine, pilocarpine and anaphylactic shock.

Diuresis : The xanthines produce an increase in urinary output. Theophylline is the most potent compound in this respect, followed by theobromine and caffeine in that order. (See Chapter 35).

Voluntary muscles : Xanthines strengthen the contraction, increase the metabolism and postpone fatigue of skeletal muscles. Caffeine is most potent in this respect. The increased ability of an individual to do more muscular work is thus due to both central and peripheral actions of caffeine. Recent work suggests that improved contractility of the diaphragm may be important in the therapeutic efficacy of aminophylline in bronchial asthma. Caffeine, when applied directly to isolated skeletal muscle, produces contracture irrespective of whether the muscle is resting or depolarized.

Miscellaneous actions: The xanthines increase the volume, acidity and pepsin content of the gastric secretion.

The basal metabolic rate is slightly increased by caffeine, probably as a result of increased metabolism of the skeletal muscles.

Theophylline also elevates plasma renin activity in man.

Absorption, fate and excretion: The xanthines are readily absorbed on oral, rectal or parenteral administration. After absorption, about 17 per cent of caffeine, 20 per cent of theophylline and 3 per cent of theobromine are bound to plasma proteins. They are metabolized in the liver, mainly by demethylation and oxidation. None of the xanthines is converted into uric acid and hence, beverages containing xanthines are not contraindicated in gout.

Mechanism of action: Methyl xanthines act probably in many ways: (1) by inhibiting cyclic nucleotide phosphodiesterase, thus preventing the conversion of cyclic AMP to 5' AMP. Following administration of methyl xanthines, tissue

concentration of cyclic AMP increases. The catecholamines which also increase the concentration of cyclic AMP by a different mechanism act synergistically with methyl xanthines; (2) by bringing about changes in the distribution of calcium at the intracellular sites and by blocking adenosine receptors. The relative contributions of these mechanisms in producing different pharmacological actions is not established.

Adverse reactions:

(i) Caffeine does not cause serious toxicity. The drug, however, may produce confusion, tremors, insomnia and excitement which may progress to mild delirium. The individual may complain of ringing in the ears, headache and may develop tachypnoea, tachycardia, emesis, fever and occasionally extra-systoles or cardiac arrhythmias. *Hence inquiry into anxiety symptoms, especially in a subject with recurrent headache, should include questions about excessive tea or coffee drinking.* The symptoms can be treated with sedatives.

(ii) The xanthine alkaloids and beverages should be administered with caution in patients with peptic ulcer. Theophylline, in such patients, may produce nausea, vomiting, epigastric pain and occasionally haematemesis, even when it is given parenterally. Local G.I. irritation can be somewhat reduced by the administration of theophylline with food.

(iii) Aminophylline, on intramuscular administration, may produce local pain, dizziness, hypotension, severe precordial pain, and even ventricular fibrillation when given intravenously. Fatalities have been reported following intravenous aminophylline. In children, aminophylline intoxication, irrespective of its route of administration, is characterized by vomiting, severe thirst, dehydration, delirium, convulsions, shock and death.

(iv) **Tolerance:** Tolerance develops after prolonged use of xanthines, mainly to their cortical stimulant, diuretic and peripheral vasodilator effects. Cross tolerance among the xanthines is

common. Xanthine tolerance is usually abolished after abstinence from xanthine beverages for a period of 8 to 10 weeks.

(v) **Habituation:** Habituation to xanthine beverages is extremely common. However, it does not seem to be dangerous.

Preparations and dosage:

(i) Caffeine citrate I.P. is a white powder with a bitter, acidic taste, soluble in water. Dose: 120 to 600 mg. orally.

(ii) Caffeine and sodium benzoate is water soluble and available in ampoules containing 250 mg. per ml. Dose: 250 to 500 mg.

(iii) Aminophylline: See Chapter 23.

Therapeutic uses:

(a) **Stimulant:** Caffeine in the form of coffee or tea is often employed for relief from fatigue and mild depression.

(b) **Headache:** Because of its action on the cerebral blood vessels, caffeine is used along with ergotamine tartrate for relief of migraine.

(c) **Acute left ventricular failure:** Aminophylline is a useful adjuvant in the treatment of paroxysmal nocturnal dyspnoea associated with left ventricular failure. Aminophylline increases the cardiac output, reduces the pulmonary artery pressure and the cardiac preload, induces bronchodilatation, stimulates the respiratory centre and causes diuresis. When the distinction between dyspnoea due to acute left ventricular failure (cardiac asthma) and bronchial asthma is not certain, it is safer to administer intravenous aminophylline rather than adrenaline (which is dangerous in the former condition) or morphine (which is dangerous in the latter condition). It is administered *slowly* intravenously in the dose of 500 mg. along with other treatment such as morphine, oxygen and phlebotomy.

(d) As a coronary dilator (See Chapter 27).

(e) In bronchial asthma (See Chapter 23).

(f) As a diuretic (See Chapter 35).

(g) Theophylline and caffeine have been shown to be effective analeptics in the treatment of primary apnoea of prematurity.

AMPHETAMINE: Amphetamine and methamphetamine are sympathomimetic amines. Their central actions are similar to xanthines but peripherally they produce adrenaline like actions. These drugs are discussed in Chapter 14.

PIPRADROL AND METHYLPHENIDATE are mild psychomotor stimulants and are discussed in Chapter 11.

(B) STIMULANTS OF THE BRAIN STEM AND MEDULLARY CENTRES

These drugs in large doses produce clonic convulsions followed by tonic convulsions. The latter are characterized by sustained contraction of all the muscles and opisthotonus or arching of the back with extension of the legs but flexion of the arms. The reason for this posture is the dominance of the extensors in the back and the legs and flexors in the arms over the antagonistic group of muscles.

PICROTOXIN: Picrotoxin is a non-nitrogenous substance obtained from the seeds of fishberry plant *Anamirta cocculas*. Picrotoxin is a powerful stimulant of the brain stem and the spinal cord and in toxic doses produces clonic convulsions in mammals. Convulsions are triggered by tactile or auditory stimuli. The drug, besides stimulating respiration, often produces salivation, emesis and rise of blood pressure by stimulation of the vasomotor centre. It acts by antagonizing the inhibitory transmitter GABA in the CNS. The drug is no more used because of its toxicity.

PENTYLENETETRAZOL (Leptazol I.P., Cardiazol) : This drug is less toxic than picrotoxin. It is a direct stimulant of the respiratory and the vasomotor centres. It does not stimulate the myocardium nor has it any significant action on the blood vessels. The onset of action is quicker than with picrotoxin. It is usually administered intravenously, in the dose of 0.5 to 1 ml. of 10

percent solution. In large doses it produces clonic convulsions. Its mechanism of action is not known. The drug was previously employed in convulsant therapy for certain types of mental illness but is now replaced by electroconvulsive therapy. It is occasionally employed to activate epileptogenic focus in E.E.G. in the diagnosis of latent epilepsy.

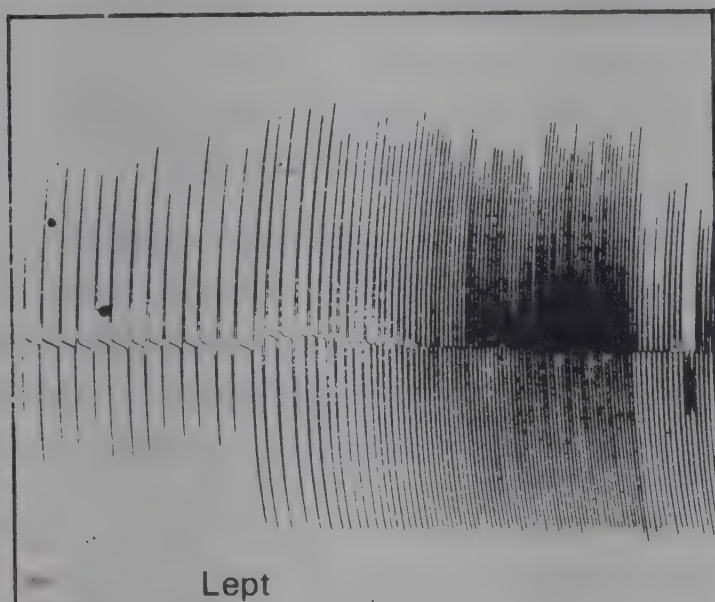


Fig 10.1 : Effect of Leptazol on respiration in dog under barbiturate anaesthesia.

NIKETHAMIDE (Coramine) : Nikethamide is a safer analeptic than either picrotoxin or pentylenetetrazol. It is structurally related to nicotine and exerts mild anti-pellagra activity.

Nikethamide stimulates the central nervous system. It stimulates respiration both directly and reflexly through the carotid sinus. The drug has no significant action on the cardiovascular system in small doses. Toxic doses may cause hypertension, tachycardia, vomiting, coughing, tremors, hyperpyrexia, arrhythmias, muscular rigidity, and tonic and clonic convulsions.

Nikethamide is not very effective orally and has to be administered by intramuscular or intravenous route for respiratory stimulation. Nikethamide injection I.P. is a sterile solution of 25 percent w/v of nikethamide in water. The dose is 1 to 4 ml. but sometimes as much as 20 ml. have been administered intravenously. The duration of respiratory stimulation following a single I.V. dose seldom lasts for more than 5-10 minutes.

DOXAPRAM : This is a non-specific analeptic used mainly as a respiratory stimulant in the post-anaesthetic period and in patients with hypoventilation. It has a wider margin of safety than nikethamide. It is administered by intravenous drip in the total dose of 0.5-1.5 mg. per kg. at the rate of 5 mg. per minute. A single intravenous injection (0.7 mg. per kg.) produces peak action in 2 minutes lasting for 5-10 minutes. Doxapram is claimed to prevent morphine induced post-operative pulmonary complications. Hence, it is presently preferred to other available analeptics, for this purpose. Serious adverse reactions include hypertension, tachycardia, arrhythmias, muscle twitchings, tremors, convulsions and vomiting.

Doxapram and nikethamide have been used as temporary measures to correct acute respiratory insufficiency in patients with chronic obstructive pulmonary disease.

CAMPHOR : Given parenterally, it is a central stimulant and can cause convulsions in large doses. Applied locally by rubbing, it acts as an irritant and a rubefacient; but gentle application produces a feeling of coolness. It is no more advocated as a respiratory stimulant. Camphor is mainly used locally in the form of liniment for its antipruritic and counterirritant properties.

CARBON DIOXIDE : See Chapter 68.

Other CNS stimulants such as amiphenazole (Daptazole), prethicamide (Micoren) and ethamivan are now rarely used because of their narrow margin of safety.

Therapeutic uses of analeptics : Analeptics have been employed for the treatment of :

(i) Chronic hypoventilation with CO_2 retention secondary to pulmonary disease, especially when it is aggravated by oxygen therapy.

(ii) Respiratory failure in the newborn.

(iii) Respiratory failure due to overdosage of the central depressants.

(iv) Post-anaesthetic respiratory depression.

Probably, the prime indication for the use of respiratory stimulants such as doxapram is in the treatment and prevention of increasing CO₂ retention and CO₂ narcosis following oxygen therapy in patients with chronic lung disease. The use of analeptics for neonatal asphyxia has met with dubious success. Other measures like prompt suction of the tracheobronchial tree and administration of oxygen or mouth to mouth breathing are more useful. The use of analeptics in the treatment of narcotic poisoning is now not recommended. In order to avoid post-anaesthetic respiratory complications, frequent turning, and making the patient cough and breathe deeply have become a part of the routine post-operative care. A selective stimulant of the respiratory centre, if available, would certainly aid this 'stir-up' regimen. However, the routine administration of nonspecific analeptics to all patients after surgery does not appear necessary or logical.

(C) STIMULANTS OF THE SPINAL CORD

STRYCHNINE : Strychnine is an alkaloid obtained from the button-shaped seeds of the plant *Strychnos nuxvomica*. The compound, after administration either orally or parenterally in animals, produces convulsions characterised by tonic extension of the body and opisthotonus. Death may occur as a result of asphyxia after seizures.

Strychnine acts mainly on the spinal cord though the drug is capable of stimulating the entire neuraxis in large doses.

Strychnine abolishes reciprocal inhibition between the antagonistic groups of muscles and augments the level and spatial distribution of the reflex excitability of the spinal cord. This enables a simple sensory (auditory, visual or tactile) stimulus to elicit a maximum tonic seizure response. It is believed to act as a competitive antagonist of the inhibitory transmitter glycine at the post-synaptic inhibitory sites. Excessive

stimulation is followed by depression and death. Because of its high and often fatal toxicity, strychnine has no place in therapeutics.

The most urgent need in the treatment of strychnine poisoning is the control of convulsions. Intravenous diazepam (10 mg. in adults, repeated as necessary) is distinctly superior to short-acting barbiturates for this purpose. All forms of sensory stimulation must be avoided. Tracheal intubation and assisted ventilation are indicated if adequate ventilation is not restored by the control of convulsions. Only after controlling the convulsions should a gastric lavage be performed. The universal antidote (powdered charcoal 2 parts, magnesium oxide 1 part and tannic acid 1 part), if administered without delay, would adsorb the alkaloid and prevent its systemic absorption. Alternatively, oxidizing solutions like 1 : 1000 potassium permanganate or 2 per cent tannic acid (as strong tea) may be employed.

II REFLEX STIMULANTS OF THE CENTRAL NERVOUS SYSTEM

LOBELINE : Lobeline is an alkaloid obtained from the leaves of *Lobelia inflata*. Lobeline and nicotine stimulate the central nervous system through the chemoreceptors of the carotid sinus. In addition to reflex stimulations of the central nervous system, lobeline stimulates autonomic ganglia, and the axon reflex which induces sweating. It is now rarely used as a respiratory stimulant.

Other reflex stimulants of the central nervous system such as nicotine, veratrum and apomorphine are discussed elsewhere. **Liquor ammonia** and smelling salts (ammonium carbonate) inhalation in syncope is a common household procedure which stimulates the respiratory and vasomotor centres reflexly.

11 Psychopharmacology

The term 'tranquillization' or 'ataraxia' has been defined in various ways and does not have any pharmacological basis; it is considered more or less synonymous with 'peace of mind'. Obviously, such a state can be produced by many drugs, depending upon the cause of disturbed 'peace of mind'. The term 'tranquillizer' was used originally to describe the psychic effect of reserpine and chlorpromazine which have the ability to *calm without causing hypnosis* or anaesthesia. Now, under the general heading of tranquillizers are included various drugs with widely differing types of pharmacological activities. Regardless of various terminologies, the objective of drug therapy in psychiatry is to induce an improved mental state in mentally disturbed patients. Drugs which selectively modify the behaviour pattern are known as 'psychotropic' or 'psychoactive' drugs. Since so little is known about the pathophysiology of mental illness, the drug treatment of mental disorders still remains essentially empirical.

It is extremely difficult to define what constitutes 'psyche' or 'mind' which is supposed to carry out three functions :

- (a) reception of environmental stimuli (cognition),
- (b) analysing the information received and formation of a reaction pattern (affect), and
- (c) the actual behavioural response (conation).

Little is known about the neurophysiological differences between normal individuals and mentally ill patients, nor is the biochemical basis for various psychiatric disorders known. The exact site and mode of action of various psycho-

therapeutic agents, therefore, remain unidentified.

Evaluation of psychotropic drugs in animals: Models of psychic disturbances analogous to those seen in humans cannot be produced in animals. Further, the intellectual superiority of man over the highest primate is so great that it is difficult to predict usefulness of drugs in the treatment of human mental illnesses from the behavioural studies in animals. It is not surprising, therefore, that therapeutic application of many compounds in humans originated from accidental observations in patients getting such drugs for other purposes. Although the vast majority of animal experiments in psychopharmacology have limited relevance to the ultimate clinical usage of drugs in human psychiatry, such pre-clinical screening in animals sometimes gives useful information. The behavioural effects of a drug can be studied in animals as follows :

(1) **Natural behavioural patterns:** Quieting property of a drug can be demonstrated by its taming effect on an aggressive monkey or on a cat in the presence of a mouse. Similarly, the modification of natural activities of various animals including mice, rats and others by drugs is helpful in evaluating their general stimulant or depressant properties.

(2) **Spontaneous motor activity:** This is usually studied in rats and mice. The animal is kept in a cage through which a beam of light passes. An electronic device records the number of times the beam is interrupted by movements of the animal. Spontaneous activity is also measured

by using a jiggle cage. It is a cage suspended on springs and hence produces oscillatory movements every time the animal moves; these can be recorded by a suitable recording device.

(3) **Motor coordination and muscle tone:** Preliminary screening for behavioural pattern will usually reveal drug-induced ataxia. This can be quantified by using the rotating rod test. A horizontally mounted rod with a diameter of 2-3 cm. is used for this purpose. Normal mice are able to maintain their position on the rod for at least five minutes while ataxic mice fall off earlier.

(4) **Drug induced behavioural patterns :** The drug effect can also be studied on various drug induced abnormal behaviour patterns in animals. Thus, web building by spiders can be altered by the administration of certain drugs like lysergic acid diethylamide (LSD) which produce psychosis in humans. Drug effects in spiders given LSD can thus be studied by observing the changes in web patterns.

Toxicity of amphetamine is considerably higher when tested on mice kept together in the same cage than on animals kept individually in separate cages. Certain drugs like phenothiazines reduce this 'group toxicity'.

Administration of reserpine in animals induces a condition somewhat resembling retarded depression in man, where there is general reduction in activity, slowing of movements, reduced responsiveness to stimulus and neglect of activities such as feeding and sexual behaviour. Such 'model illness' in animals has been widely used for testing the antidepressant properties of drugs.

Behavioural changes produced by drugs can also be studied in surgically produced abnormal behavioural patterns in animals. Thus, mice and rats can be made aggressive by producing lesions in a part of their limbic system. Similar aggressive behaviour can also be induced by applying small electric shocks to the floor of their cage.

(5) **Learning and discrimination behaviour:** The maze has provided the psychological setting for most of these studies. Thus, drug

effect on maze learning or on perfected maze habit in animals, using the time required for performance as a criterion, can give some idea about the influence of a drug on learning and discrimination behaviour.

(6) **'Emotional behaviour' and 'conditioned neurosis':** The problem of experimental neurosis is well-known since the work of Pavlov. The drug effect has been studied on a variety of induced 'neurotic' reactions (phobias, compulsions and regressions) in animals like rats and cats

Drugs expected to inhibit selectively certain abnormal reactions or behaviour patterns such as fear and/or anxiety, without impairing the innate behaviour, are studied in 'conditioned animals'. In *conditioned avoidance* the animal first learns a response like running, pressing a bar or climbing up a pole in order to escape from an electric shock. Then it learns to avoid the shock by responding promptly to a danger signal such as a buzzer sound which precedes the shock. Certain drugs like chlorpromazine selectively block such conditioned responses but not the non-conditioned ones, where the animal still escapes once the shock is applied. Barbiturates, on the contrary, abolish both conditioned and non-conditioned avoidance responses.

(7) Effects of drugs on behaviour are also studied by implanting or injecting them directly into various parts of the brain.

The psychotropic drugs that reduce the spontaneous locomotor activity and the exploratory activity in the maze, inhibit conditioned avoidance responses, prolong barbiturate anaesthesia and cause some ataxia are likely to be useful as antipsychotic drugs. The animal pharmacologic test that correlates best with antipsychotic activity is the prevention of apomorphine (a dopamine agonist) induced vomiting in dogs. The depressant drugs which reduce aggressiveness but increase the exploratory activity in a maze without causing ataxia are likely to be useful in anxiety states.

Drugs with possible application as antidepress-

sants usually potentiate the actions of amphetamine and increase the spontaneous motor activity.

For the evaluation of psychotropic drugs in man a large number of rating scales have been designed to obtain an overall assessment of the mental state and to quantitate the drug induced modification of such parameters as anxiety, depression or the side effects of drugs. Rating scales can be used to assess both objective and subjective features of the condition.

Classification : Psychoactive drugs can be classified as :

I. Antipsychotics —used mainly in major psychoses like schizophrenia,

(a) Phenothiazine derivatives e.g. chlorpromazine.

(b) Rauwolfia alkaloids, e.g. reserpine.

(c) Butyrophenone derivatives e.g. haloperidol, trifluoperidol.

(d) Diphenylbutylpiperidines e.g. pimozide, penfluridol and fluspirilene.

(e) Thioxanthene derivatives e.g. chlorprothixene and thiothixene.

(f) Indolic derivatives e.g. molindone.

(g) Miscellaneous compounds e.g. oxypertine, tetrabenazine.

These drugs are also called 'Major tranquillizers' because they reduce the agitation and disturbed behaviour often associated with delusions and hallucinations in schizophrenia or senile illness.

II. Anti-anxiety agents - mainly useful in anxiety states and neurosis, e.g. meprobamate, benzodiazepines, chlormethiazole and buspirone.

These drugs are sometimes called as 'Minor tranquillizers' because they have a calming effect in anxiety states associated with neurotic personality, situational crisis or physical disease.

III. Anti-depressants also called as mood elevators or psychic energisers such as (a) Monoamine oxidase (MAO) inhibitors. (b) cyclic antidepressant compounds e.g. imipramine and amitriptyline. (c) Lithium carbonate and (d) Caffeine like drugs.

IV. Psychogenic drugs which induce

behavioural abnormalities resembling psychosis e.g. LSD and mescaline.

ANTIPSYCHOTIC DRUGS

PHENOTHIAZINE COMPOUNDS : These are the most widely used compounds in the treatment of major psychoses. The first important drug chlorpromazine was synthesized in 1950 and was shown to possess an amazingly large number of actions. Its introduction into psychiatric practice by Delay and Deniker in 1952 marked the beginning of modern psychopharmacology. Phenothiazine has a three ringed structure in which two benzene rings are linked by a sulphur and nitrogen atoms. According to the chemical structure, phenothiazines could be predominantly antipsychotic, anticholinergic or antihistaminic.

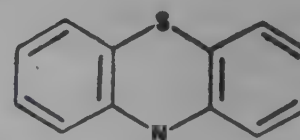


Fig. 11.1: Phenothiazine nucleus.

All the phenothiazines used in psychiatry have a three carbon bridge between the ring and the side chain nitrogen atom.

Since chlorpromazine is the most extensively studied and used antipsychotic phenothiazine it is discussed in detail here. Other antipsychotic phenothiazine drugs differ from chlorpromazine mainly in potency and to a certain extent in their profile of actions. Hence, the important differences between these compounds and chlorpromazine are pointed out.

Pharmacological actions of chlorpromazine:

Behavioural effects : When chlorpromazine is administered to a normal monkey, the animal loses its aggressiveness, its interest in the surroundings and in food, and shows indifference

to happenings around. There is a complete lack of initiative. The animal does not attack spontaneously; instead, it sits motionless. There is no change in the state of wakefulness and consciousness and the control over the muscles remains unaffected.

In patients with major psychosis with agitation, chlorpromazine produces psychomotor slowing, emotional quietening, diminution of initiative and anxiety, without affecting wakefulness (Neuroleptic Syndrome). The subject will sit in silence and show indifference to the events around him, responding minimally to external stimuli. Although some of these effects resemble the sedative effects produced by barbiturates, tolerance develops rapidly to this sedative action. The antipsychotic effect resulting in amelioration of symptoms, however, continues. Furthermore, unlike with barbiturates, there is little ataxia and incoordination.

Chlorpromazine effectively blocks the conditioned avoidance responses, so that the animal forgets what it has learnt but, unlike after barbiturates, still escapes to safety as soon as a shock is felt. The drug relieves experimental neurosis.

Phenothiazines produce their antipsychotic effect probably by affecting three of the major integrating systems of the brain. Firstly, they may reduce the incoming sensory stimuli by acting on brain stem reticular formation. The drugs also modify the function of the limbic system. Lastly, they are known to cause blockade of post-synaptic monoaminergic (noradrenaline, dopamine and 5-hydroxytryptamine) transmission in the brain, thus leading to a decrease in the central sympathetic activity. It is believed that the therapeutic efficacy of the antipsychotic drugs is mostly related to their ability to block the dopaminergic receptors in the mesolimbic system. There are two different subpopulations of dopamine post synaptic receptors namely D1--linked to the stimulation of the activity by adenylate cyclase and D2--with negative association with this enzyme. Presynaptic dopamine receptors or auto receptors have also been demonstrated in the brain. These autorecep-

tors appear to modulate the rate of dopamine biosynthesis by a negative feed-back metabolism. Neuroleptics probably act by binding at D2-subpopulation. A similar blockade of dopamine action in the corpus striatum is responsible for the extrapyramidal reactions so often associated with antipsychotic drugs. Chlorpromazine has been shown to get concentrated in the limbic, hypothalamic and cortical areas; hence, some degree of cortical depression may also occur.

Other CNS actions: Spontaneous motor activity is diminished and with larger doses, a state of catalepsy is produced where the body and limbs are moulded into various postures and remain immobile for prolonged periods. Catalepsy resembles but is not the same as catatonia seen in some schizophrenics; the latter is relieved by phenothiazines.

Phenothiazines potentiate the action of analgesic drugs like morphine and prolong hexobarbitone sleep in animals. In suitable doses they can produce sleep with characteristic slow wave pattern in E.E.G.

Unlike barbiturates, phenothiazines have no specific anticonvulsant action and in animals they have no protective effect against convulsive properties of leptazol, picrotoxin and strychnine. In fact they increase strychnine toxicity and can precipitate seizures in epileptics.

Antiemetic action : Chlorpromazine depresses the chemoreceptor trigger zone (C.T.Z.) and thus acts as a powerful antiemetic. It, however, is not effective in vomiting due to vestibular stimulation or that caused by local gastrointestinal irritation. It counters the effects of apomorphine (a dopamine receptor stimulant) on the CTZ in the medulla.

Autonomic nervous system : Chlorpromazine possesses distinct alpha adrenergic blocking effect and can thus block certain actions of adrenaline and noradrenaline. It also produces moderate inhibition of actions of acetylcholine and 5-hydroxytryptamine. It has a central depressant action on the hypothalamic centre controlling sympathetic activity.

Cardiovascular system : Chlorpromazine sometimes produces orthostatic hypotension which is probably due to inhibition of centrally mediated pressor reflexes along with peripheral adrenergic blocking actions. It also dilates the blood vessels directly.

It is myocardial depressant and may cause defects in intra-ventricular conduction. Thus, it produces prolongation of QT interval and blunting of T waves in the E.C.G.

Endocrines : Chlorpromazine can block ovulation, suppress oestrous cycle and can produce amenorrhoea and lactation in women. It diminishes the libido in men. These actions are probably due to blocking of dopamine action on the hypothalamus and the pituitary. Dopamine, acting directly on the pituitary, inhibits prolactin release. Chlorpromazine also blocks the release of growth hormone.

Miscellaneous effects : It has a potent local anaesthetic action. It is claimed to possess skeletal muscle relaxant action in some spastic disorders; the mechanism of such action, however, is unknown. It prevents the shivering response to cold and thus favours the development of hypothermia.

Tolerance : In psychiatric practice, tolerance to the sedative effect of chlorpromazine and other phenothiazines may develop. However, tolerance for the antipsychotic effect of these compounds has not been observed.

After sudden cessation of treatment with phenothiazines, withdrawal nausea and vomiting may develop in as many as 30 per cent of individuals. Muscular discomfort, exacerbation of psychotic states and insomnia have also been reported. Although some degree of dependence on phenothiazines has thus been accepted, true drug dependence to these compounds has not been demonstrated. The characteristic craving is absent and the withdrawal symptoms are essentially mild.

Absorption, fate and excretion: Phenothiazines are well absorbed on oral and parenteral administration. A very active enterohepatic

circulation increases the duration of action and prolongs the biological half life of chlorpromazine. Thus, chlorpromazine or its metabolites can be detected in urine even 6 to 12 months after discontinuation of therapy in psychiatric cases. Chlorpromazine is usually given by mouth. When injected intramuscularly, it may produce local irritation and pain.

After absorption, phenothiazines are distributed in all the body tissues. Brain concentrations are lower than those in other organs, but are much higher than the plasma concentrations.

Chlorpromazine and other phenothiazines are metabolized in the liver by hydroxylation and subsequent glucuronide conjugation, sulfoxidation and demethylation.

Adverse reactions : Apart from common effects such as nasal stuffiness, dryness of mouth and palpitation, these include:

(a) **Intolerance :** Skin eruptions of various types, photo-sensitivity and contact dermatitis have been reported.

Another type of pigmentation resulting in yellowish brown or purple discolouration of the exposed skin develops in individuals on prolonged therapy with large doses of phenothiazines. The colour is attributed to melanin or melanin like substance formed by the phototoxic action of sunlight acting on the phenothiazine in the skin. The pigment also occurs in the melanocytes and in several organs like brain, liver, kidneys, retina and the cornea. Serious effects due to visceral involvement are possible. Thus, visual impairment and near blindness may occur with pigmentary retinopathy. Sudden unexplained death in healthy individuals on phenothiazines therapy has been linked with visceral pigmentation.

(b) **Extrapyramidal effects :** A large number of patients receiving phenothiazines show extrapyramidal symptoms of parkinsonism viz tremor, muscular rigidity, excessive salivation and akinesia. These are due to blocking of dopamine receptors in the basal ganglia and can be countered by anticholinergic drugs such as

benzhexol but not by levodopa or amantidine. Motor restlessness, akathisia, acute dystonic reactions and tardive dyskinesia can also occur.

(c) **Central nervous system** : The behavioural reactions with phenothiazines include drowsiness, impaired psychomotor function, restlessness, excitement, psychotic reactions and toxic confusional states. Fortunately, most of the patients tolerate these drugs well and such reactions are rarely serious. However, depression, which often has an 'endogenous' character may develop after the patient has been on therapy for many weeks. Such depression should be treated with tricyclic antidepressant drugs or ECT, and phenothiazines reduced or stopped.

The phenothiazines may occasionally produce epileptic seizures (particularly in individuals with history of seizures), disturbances in temperature regulation (a mild rise in body temperature or hypothermia) and respiratory irregularities, when administered in large doses. The effects, however, are reversible on discontinuation of therapy.

(d) **Autonomic nervous system** : The phenothiazines, by virtue of their anticholinergic activity, may produce blurring of vision, tachycardia, constipation or even paralytic ileus, difficulty in micturition and sometimes inhibition of ejaculation. Postural hypotension can occur. Marked hypotension is uncommon but hypotensive crises on parenteral administration have been observed particularly in the elderly. Concomitant use of alcohol predisposes to this effect. *Chlorpromazine should not be given intravenously*, as fatalities due to a sudden fall in blood pressure have been reported.

(e) **E.C.G. Changes** : Thioridazine and chlorpromazine can induce E.C.G. alterations resembling those caused by quinidine and by hypokalemia. Caution should be exercised in the use of these agents in individuals with cardiac disease.

(f) **Haemopoietic system and the liver** : Phenothiazines may produce agranulocytosis in 0.5 per cent of individuals. The drugs may rarely produce thrombocytopenia and aplastic anemia.

Intrahepatic obstructive (cholestatic) jaundice occurs in about 0.5 to 2 per cent of the patients receiving chlorpromazine. It is probably allergic in origin. Jaundice usually appears within first 6 weeks of therapy, but may develop much later in some cases. Almost all the patients recover completely and spontaneously.

Administration of phenothiazines to mothers during pregnancy has been associated with a significantly increased incidence of neonatal jaundice.

(g) **Endocrinal and metabolic disturbances** : Long term therapy may occasionally produce gynaecomastia, lactation and menstrual irregularities. Aggravation of diabetes mellitus, impotence and weight gain as a result of increased food intake have been reported.

(h) **Interaction with other drugs** : The phenothiazines prolong and intensify the depressant effect of a number of narcotics including the barbiturates, morphine, pethidine and alcohol. Dangerous and bizarre reactions may be precipitated if phenothiazines are used in combination with MAO inhibitors. Serious hypotension may occur with other hypotensive drugs such as reserpine, methyldopa, mecamylamine and phenolamine whereas the phenothiazines may neutralize the hypotensive action of guanethidine and clonidine.

The following are equipotent in their neuroleptic effect when given orally; chlorpromazine 100 mg, chlorproxithene 100 mg., thioridazine 100 mg; trifluoperazine 5 mg; haloperidol 2 mg, fluphenazine 2 mg. Acute schizophrenic reaction needs initiation of treatment with the equivalent of 400 mg of chlorpromazine per day given in four divided doses. On subsequent days, the dose is increased by the equivalent of 200 mg of chlorpromazine till the acute reaction is controlled. The maintenance dose for the prevention of recurrence in chronic schizophrenics is the equivalent of 100-300 mg of chlorpromazine per day.

In general, the incidence of neurological adverse reactions is higher with the more 'potent'

Table 11.1 : Some commonly used phenothiazine derivatives

Compound	Chemical structure of the side chain	Pharmacological properties	Daily dose (mg)	Therapeutic uses
Group I				
Chlorpromazine (Largactil)	Propyldimethylamino	Marked sedative and autonomic effects		Refer to the text
Promazine (Sparine)	Propyldimethylamino	Marked autonomic, moderate E.P. and antiemetic effects	500 to 1000	Antipsychotic; antiemetic
Triflupromazine (Siquil)	Propyldimethylamino	Marked E.P., high antiemetic and low autonomic effects	100 to 300 10 to 30	Antipsychotic; antiemetic
Group II				
Thionidazine (Mellaril)	Piperidine	Moderate sedative and autonomic, less E.P. and antiemetic effects. Retinopathy reported.	50 to 500	Antipsychotic
Mesoridazine (Serentil)	Piperidine	Marked sedative, less E.P., moderate autonomic effects.	100 to 400	Antipsychotic
Group III				
Fluphenazine (Anatensol)	Piperazine	Moderate sedative, marked E.P. and less autonomic effects.	2 to 10	Antipsychotic
Trifluoperazine (Eskazine)	-do-	Less sedative, less autonomic and marked E.P. effects	5 to 15	Antipsychotic
Perphenazine (Trilafon)	-do-	Moderate sedative, marked E.P. and less autonomic effects	15 to 30	Antipsychotic
Prochlorperazine (Stemetil)	-do-		25 to 100	Antipsychotic. antiemetic
Thiethylperazine (Torecan)	-do-		6.5 mg (base*)	Antiemetic
Group IV				
Diethazine (Diparcol)	Ethyldiethylamino	See Chapter 19		} Parkinsonism
Ethapropazine (Parsidol)	Ethyldiethylamino			
Group V				
Promethazine (Phenergan)	Ethyldiethylamino	See Chapter 20		Antihistaminic
* Single dose	E.P. = extrapyramidal			

neuroleptics such as haloperidol, trifluoperazine and fluphenazine; on the other hand, the incidence of orthostatic hypotension is higher with the less 'potent' neuroleptic drugs such as chlorpromazine.

Preparations and dosage:

(i) Chlorpromazine hydrochloride I.P. is available as tablets containing 10, 25, 50 and 100 mg. of the drug, as a syrup containing 25 ml (for adults) and 5 ml (pediatric) per ml and as suppositories. The dose varies considerably, according to the indication and the condition of the patient. The usual range is 25 mg. to 1000 mg.

(ii) Chlorpromazine injection I.P. contains 25 mg. of the drug per ml. It is usually administered intramuscularly in the dose of 25 to 50 mg. The patient should be confined to bed for 30 minutes following intramuscular injection in order to avoid postural hypotension.

(iii) The phenothiazines divided according to the side chain attached to the nitrogen atom are listed in Table 11.1

(iv) '*Depot*' phenothiazines : Esters (such as decanoate, enanthate and palmitate) of fluphenazine, perphenazine, flupenthixol and oxyprothepine when given I.M. or S.C. release the active drug slowly. Satisfactory therapeutic response in schizophrenia could be obtained by injecting fluphenazine decanoate in the dose of 12.5-50 mg. every 2 to 4 weeks.

Therapeutic uses :

(a) **Schizophrenia** : Chlorpromazine and its analogues are most effective in psychotic patients who are excited, agitated, tense and who have productive psychotic symptoms. Apathetic, driveless, nonproductive psychotics do not respond well. These drugs have revolutionized the treatment of a condition called schizophrenia, the most common of the serious mental illness.

The word 'schizophrenia' was coined from a Greek word meaning 'split mind' to describe a mental syndrome where an individual is dominated by one set of ideas or a complex to the exclusion of others. Thus, the harmonious work-

ing of the mind is split, with one portion seizing control of the rest. The schizophrenic patient, therefore, lives in his own world, dissociated from reality. He is a victim of delusions and hallucinations and believes that only his behaviour and actions are rational, without realising that he is ill. His mental functioning is sufficiently impaired to interfere grossly with his capacity to meet the ordinary demands of life. The disease is common in young people between the ages of 18 and 28, and exhibits a hereditary tendency. It may exist in several varieties and the paranoid form in which the individual becomes suspicious of and belligerent towards the entire society is perhaps the most dangerous. Etiology of schizophrenia is not clear though some biochemical basis is suspected. It may be noted that all the known antipsychotic drugs seem to block the effects of dopamine. Phenothiazines do not cure schizophrenia but exert a quietening effect on agitated patients, reduce hallucinations, aggression and anxiety and make the patient more co-operative and acceptable. Disturbed thinking, paranoid symptoms, delusions and personal neglect may improve. Although improvement with phenothiazine drugs usually commences during the first 7-21 days, it may be delayed by as much as 5-6 weeks. It is not possible to predict which cases will respond promptly and there is a proportion of patients who do not improve with phenothiazines alone but respond well to a phenothiazine and ECT combination. Patients in catatonic excitement are better controlled initially with ECT, and phenothiazine therapy started subsequently. Unless there are physical contraindications, ECT and phenothiazine can be combined in the treatment of majority of cases of schizophrenia, provided the lower convulsive threshold produced by these drugs is kept in mind. Phenothiazines have made it possible for the patients who otherwise would have needed prolonged hospitalization in mental 'asylums' to stay at home and to engage in productive activity. The oral dose of chlorpromazine varies widely from 100 to 1500 mg. per day. Highly agitated, rowdy and violent patients obviously

would need larger doses, sometimes given parenterally. Present evidence indicates no significant differences in clinical efficacy between chlorpromazine and the other important phenothiazines, although in a patient with specific symptomatology one phenothiazine may be preferred to another. Chlorpromazine may cause more drowsiness and depression while other phenothiazines may cause more extra-pyramidal symptoms which might need treatment with antiparkinsonian drugs. Drugs like thioridazine cause few extra-pyramidal reactions probably because their own antiparkinsonian activity due to their greater ability to block central muscarinic receptors. Patients who cannot be relied upon to take the drug properly can be treated with weekly to biweekly injections of 'depot phenothiazines'. These dosage forms are particularly useful in uncooperative patients, for maintenance therapy of chronic psychoses and during relapse. After the therapeutic result is obtained, the drug should be continued without interruption in smaller maintenance doses for a long time. Daytime drowsiness may interfere with the patient's ability to work, but this could be reduced if he takes most of his daily dose at night. The withdrawal should be slow (6-12 months) as reappearance of symptoms following withdrawal is not uncommon. A longer maintenance period is particularly recommended in patients with a history of relapse. Combinations of various phenothiazines have not been shown to be superior to adequate doses of individual drugs.

(b) **Senile psychosis** : The phenothiazines are sometimes useful in senile psychosis for controlling delusions and hallucinations. They can also be used during withdrawal of alcohol and narcotic drugs in addicts. However, their wide and indiscriminate use in anxiety and tension in all types of psychiatric disturbances must be deplored.

(c) **Maniac depressive psychosis** : Chlorpromazine and haloperidol are both effective in the treatment of mania and can be combined with lithium therapy. (See later.)

(d) **Behavioural disorders in children**:

Phenothiazines are sometimes used to control the excessively aggressive and destructive behaviour in children in whom they produce a quietening effect. In such cases, other causes of aggressiveness such as temporal lobe epilepsy, schizophrenia, hypoglycemia and drug (amphetamine) abuse should be ruled out.

(e) **Antiemetic and antihiccough** : Chlorpromazine is useful to control vomiting due to uraemia, radiation sickness and certain drugs. Chlorpromazine has also been employed in the treatment of nausea and vomiting of pregnancy but the other phenothiazines are usually preferred. Chlorpromazine is not effective in motion sickness.

Chlorpromazine is effective in the treatment of intractable hiccough. The mechanism of this effect, however, is unknown.

(f) **Miscellaneous** : Chlorpromazine is employed for preanaesthetic medication.

RAUWOLFIA ALKALOIDS : The plant *Rauwolfia serpentina* (Benth) is a climbing shrub indigenous to India. It was named so in honour of Dr. Leonard Rauwolf, a 16th century botanist who probably was never aware of its existence. In ancient Ayurvedic medicine, the extract of this plant has been claimed to be useful in cases of hypertension, insomnia, insanity and even snake bite. It is called serpentina because of the resemblance of the root to a snake.

From amongst the various alkaloids of this plant, reserpine is commonly used in therapeutics. **Pharmacological actions of reserpine**:

(a) **Central nervous system** : It has central antipsychotic actions resembling those of phenothiazines. It differs from the latter compounds in that it has no antihistaminic, cholinergic blocking or direct adrenergic blocking effects. In man, it produces a similar calming effect as well as extrapyramidal actions as those observed following chlorpromazine. Unlike chlorpromazine, however, it does not produce clouding of consciousness. It also increases the potency of convulsant drugs acting on the brain.

Reserpine is of great pharmacological interest because it produces depletion of endogenous 5-hydroxytryptamine (5-HT) and catecholamines from the brain and peripheral sites. Such depletion can last for days or weeks according to the animal species studied. A single dose of 5 mg./kg. body weight is sufficient to cause 90 per cent reduction in brain 5-HT and noradrenaline over a period of 10 days. This depletion of cerebral monoamines is believed to be responsible for its central actions. However, the evidence regarding the relative importance of various amines in this respect is not clear. It appears that the drug acts by more than one mechanism.

Reserpine is less effective than phenothiazines in the treatment of schizophrenia. In addition, it may give rise to epileptic convulsions and severe mental depression precipitating suicidal tendencies; hence, it is no more favoured as an antipsychotic drug.

(b) **Cardiovascular system** : Reserpine is commonly used as an antihypertensive drug. See Chapter 26.

HALOPERIDOL (Serenace) : This is a very potent drug, belonging to the class of butyrophenones but with similar clinical effects as piperazine phenothiazines. It has less prominent sedative and autonomic effects than chlorpromazine. It has been claimed to be more effective in highly agitated or maniac patients. It is given orally in the dose of 1.5 to 4.5 mg. three times a day. The incidence of extrapyramidal effects with this drug is high and it does not seem to be superior to phenothiazines in the treatment of schizophrenia. The other drugs of this series are trifluoperidol (Triperidol) and droperidol.

DIPHENYL-BUTYL PIPERIDINES : Pimozide (2-8 mg) once daily may have the advantage in that the prescribed dosage can be almost covered under supervision. Penfluridol, structurally related to haloperidol, has a long duration of action when given orally, and has been used in the dosage of 20-100 mg once a week.

Orally active, long-acting neuroleptics may be useful in practice to eliminate failure of patient compliance.

Various other drugs like pericyazine, benzquinamide, chlorprothixene, clopenthixol, cenbutandol, molindone, prothipendyl and sulpiride have been shown to be pharmacologically active. They mainly differ in their pharmacokinetic properties and in their sedative, autonomic and extrapyramidal effects. Unlike other neuroleptics which react with dopamine (D1 and D2) receptors, sulpiride is claimed to be specific antagonist at post-synaptic D2 receptors.

ANTI-ANXIETY DRUGS

As a group, anti-anxiety drugs (Anxiolytics) have pharmacological actions similar to those of the older sedatives. Their CNS depressant effect is dose dependent. In smaller doses, they relieve anxiety while in larger doses they induce sleep and can, therefore, be grouped together with sedative hypnotics. Because of their depressant effect on the motor cortex, many of them also act as anti-convulsants.

MEPROBAMATE (Equanil, Miltown) : This is a simple aliphatic compound, a propanediol derivative, bitter in taste and relatively insoluble in water.

Pharmacological actions: Administered to patients with anxiety, it relieves tension, fear and tremulousness, removes hostility and produces a sense of well being. Unlike phenothiazines, it has no extrapyramidal actions or antipsychotic effects and it does not selectively suppress conditioned responses. The sedative effect of meprobamate resembles that produced by barbiturates so much, that it is sometimes classified as a sedative hypnotic. Like barbiturates, it suppresses REM sleep. The drug produces a central muscle relaxant action on the voluntary muscles and has anticonvulsant properties.

The mechanism of anti-anxiety action is not well understood. It inhibits a variety of responses

to hypothalamic stimulation. The drug has no effect on the autonomic nervous system in therapeutic doses.

In large doses, meprobamate can produce impairment of learning, motor incoordination and disturbances of reaction time.

Absorption, fate and excretion : The drug is well absorbed from the gut and peak blood levels are reached within 2 hours. Its biological half-life is about 10 hours. It is mainly metabolised in the liver and almost 90 per cent is excreted in the urine as the glucuronide of its oxidised derivative. Like barbiturates it accelerates its own degradation by liver microsomal enzymes on prolonged administration.

Adverse reactions : The commonest adverse effect is drowsiness. Rarely, it can give rise to

angioneurotic edema, allergic skin reactions and blood dyscrasias like leukopenia, agranulocytosis and aplastic anemia.

The drug can produce tolerance and drug dependence. The withdrawal syndrome resembles that produced by barbiturates and includes hallucinations, tremors, convulsions and coma.

Acute intoxication due to meprobamate produces a picture similar to that following barbiturates. The treatment is similar to that of barbiturate intoxication.

Therapeutic uses : Meprobamate is administered orally in the treatment of anxiety states and neurosis. It can also be given as a sedative-hypnotic. The dose is 400 mg. tablet, 3 to 4 times daily.

Table 11.2 : Benzodiazepine derivatives and doses

Name	Total ** daily oral dose mg
I. * Effective half-life more than 24 hrs:	
Chlordiazepoxide (Librium)	15-100
Diazepam *** (Sobride, Valium, Calmpose)	5 - 40
Flurazepam (Dalmane)	15 - 30
Prazepam (Verstran)	20 - 40
Chlorazepate (Tranxene)	15 - 60
II. Effective half-life 5-24 hrs:	
Nitrazepam (Nitravate, Hypnotex)	5 - 15
Lorazepam (Larpose)	1 - 4
Oxazepam (Serapax)	15 - 60
Temazepam	10 - 20
III. Effective half-life less than 5 hrs:	
Triazolam	0.25 - 1
Midazolam	i.v. use

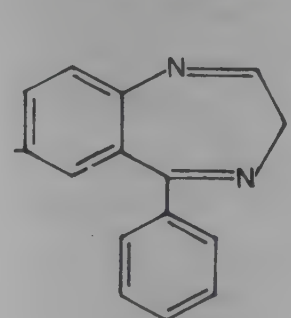
*These compounds are metabolised to clinically important active metabolites with elimination half-life values ranging between 36 and 200 hrs.

**Can be given in divided doses.

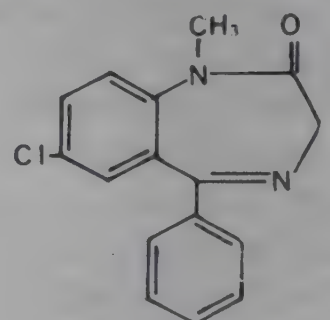
***For I.V. use, inject 5 mg directly and slowly.

BENZODIAZEPINES: Benzodiazepine derivatives are currently the most commonly prescribed anti-anxiety agents. The important members of this group are shown in Table 11.2. All anxiolytic benzodiazepines have similar properties; however, they differ in their pharmacokinetic profiles. **Diazepam** is the most commonly used drug from this group.

Pharmacological actions : (a) *Behavi-*



1, 4-Benzodiazepine
nucleus



Diazepam

Fig. 11.2

oural and antianxiety effects : In both animals and humans, benzodiazepines produce sedation, reduce aggressiveness and thus cause a calming (taming) effect. Unlike chlorpromazine, they block conditioned as well as unconditioned responses. In this respect, they resemble barbiturates and meprobamate. Clinically, they produce beneficial effects in anxious, neurotic patients.

Such therapeutic benefits are, however, difficult to assess. The mechanism of antianxiety action is not known though they act at many levels of the neuraxis. Experimentally they have been shown to act on the limbic system, the hypothalamus and the brain stem reticular system.

(b) *Hypnotic action* : See Chapter 6.

(c) *Muscle relaxant and anticonvulsant action*: They have a muscle relaxant action; a part of this effect is probably due to CNS depressant action. They increase the seizure threshold and act as anticonvulsants.

The exact mechanism of action of benzodiazepines remain speculative. They probably facilitate the inhibitory presynaptic and /or postsynaptic action of GABA. The regional distribution of benzodiazepine receptors parallels that of GABA receptors in the brain. The anti-spasticity effect appears to involve the GABA receptors in the brain stem and the spinal cord whereas the sedative and anticonvulsant activities are localized in the limbic system. Recent studies suggests that there are different types of benzodiazepine receptors in different areas of brain. Benzodiazepines also reduce the turnover of brain 5-HT and noradrenaline.

(d) *Miscellaneous actions* : The compound may lower the blood pressure and decrease the respiratory rate both in animals and in humans.

Absorption, fate and excretion : Although benzodiazepines have similar pharmacodynamic properties, they differ from each other in their pharmacokinetic characteristics. Given orally, diazepam and chlorazepate are most rapidly and completely absorbed from the proximal small intestine; prazepam and oxazepam are the least rapidly absorbed; flurazepam and lorazepam fall in between these two groups. The duration of action following a single dose also depends upon the rate and extent of drug distribution. Thus, diazepam is extensively distributed, causing prompt reduction of single dose effect. Lorazepam, on the other hand, has less extensive distribution and hence, effective concentration persist in plasma and brain for many hours after a single dose.

Many benzodiazepines are biotransformed to clinically active metabolites, some of them with longer half-life than the parent compound. Thus, desmethyldiazepam (half-life 36-200 hours), a major metabolite, plays an important role in the clinical effects of chlordiazepoxide, diazepam, prazepam, chlorazepate and medazepam. Clorazepate and prazepam are in fact pro-drugs or drug precursors, and reach the systemic circulation only as desmethyldiazepam. Flurazepam is converted to the active metabolite desalkylflurazepam. Hence, multiple dose therapy with such drugs like diazepam leads to accumulation of the long half-life, active metabolite, resulting in prolongation of effect. Diazepam, therefore, is quite suitable for once daily (bed time) antianxiety therapy. It is possible that such accumulation may cause unwanted daytime sedation. However, it should be noted that clinical drug effects do not necessarily increase in direct proportion to plasma concentration because of development of adaptation or tolerance to diazepam and similar compounds. Because of long half-life, clinically important amounts of chlordiazepoxide, diazepam or desmethyldiazepam may persist in the blood and in the body for many days or weeks after termination of prolonged therapy. This could be beneficial as it prevents the rapid return of anxiety and delays the development of withdrawal symptoms.

Benzodiazepines are metabolised in the liver and their clearance is reduced in the presence of hepatic damage, leading to prolongation of duration of action. For similar reason, their half-life is prolonged in individuals over the age of 60 years and in infants; hence, dosage should be reduced under such conditions.

Benzodiazepines like nitrazepam, bromazepam, lorazepam, temazepam and oxazepam have short half lives varying between 5 and 30 hours, and may have to be given in multiple daily doses for their anxiolytic effect. They are, however, suitable as hypnotics where residual daytime effect is unnecessary.

The absorption of chlordiazepoxide and diazepam given intramuscularly is slow, incomplete

and erratic; if desired, they can be given intravenously for rapid onset of action. Lorazepam given intramuscularly is, however, absorbed satisfactorily.

Adverse reactions : Benzodiazepines in general are well tolerated drugs. The common side effects are drowsiness, lethargy and ataxia. Patients can develop tolerance and physical dependence. Withdrawal symptoms include insomnia, agitation, depression and even convulsions. The treatment is similar to that of barbiturate dependence. The drug may occasionally produce personality changes and aggravate schizophrenia. Rarely, they may cause a paradoxical increase in hostility, irritability and anxiety.

Rarely, benzodiazepines cause allergy, photosensitization, vertigo, headache, impaired sexual function, leucopenia and menstrual irregularities. They may produce bizarre reactions with alcohol, M.A.O. inhibitors, barbiturates and amitriptyline. H₂ receptor blockers like cimetidine and the antituberculous drug INH retard the elimination of diazepam by inhibiting the hepatic microsomal enzymes. However, serious drug interactions are relatively rare with this group of drugs. They should be used cautiously in the presence of respiratory diseases. These drugs possess a dependence producing liability and are enough misused to pose public health and social problems.

Administration of benzodiazepines to the mother before delivery sometimes causes apnoeic spells, reluctance to feed, hypotonia and hypothermia in the newborn ('floppy baby syndrome').

Therapeutic uses of benzodiazepines:

- (1) In anxiety states and neuroses.
 - (2) As hypnotics (See Chapt. 6).
 - (3) During withdrawal of alcohol in chronic alcoholics.
 - (4) As anticonvulsants and in the treatment of epileptic seizures (see Chapt. 7).
 - (5) Pre-anaesthetic medication : See Chapt 5.
- I.V. medazolam with short half-life is used in anaesthesia, as a substitute for i.v. diazepam.

Flumazenil, an imidazodiazepine, binds

competitively with benzodiazepine receptors and blocks many of the pharmacologic actions of benzodiazepines. Given alone, it has minimal effect on the central nervous system. Interestingly, flumazenil will not block all the pharmacologic effects of GABA, GABA-mimetics or barbiturates but it will *specifically* antagonize the actions of benzodiazepines.

Given orally, it is rapidly absorbed and has a high hepatic clearance. It is metabolised in the liver and very little is excreted unchanged. Incremental doses upto 0.5 - 1 mg. i.v. are effective. The duration of action of a single dose varies between 15 and 140 minutes. The drug can cause withdrawal syndrome in patients dependent on benzodiazepines.

Clinically, it can rapidly reverse the central effects of benzodiazepines and has been used to reverse the effects of these drugs. I.V. flumazenil infusion can facilitate the return of consciousness within 5-15 minutes in patients with benzodiazepine poisoning.

CHLORMETHIAZOLE (Heminevrin): Chlormethiazole ethane-di-sulphonate is a thiazol derivative with sedative, hypnotic and anti-convulsant actions. When given with barbiturates and tranquillizers it produces an additive effect.

Given orally, it is absorbed rapidly. It is supplied as 500 mg. tablets.

The drug has been tried in the treatment of delirium tremens where it can be injected or given orally to induce sedation or sleep. It has also been used as an intravenous anaesthetic in combination with nitrous oxide. The typical adverse effects include tingling sensation particularly in nose and a moderate fall of blood pressure following intravenous administration. Failure to produce marked respiratory depression even in excessive doses and relation of its structure to thiazol part of thiamine molecule, make it a drug of pharmacological interest. It has also been used as a hypnotic in the elderly.

There are many other non-barbiturates sedatives like hydroxyzine hydrochloride (Atarax), chlormezanone (Trancopal), diphenhydramine

and buclizine hydrochloride available in the market. Some of these, like hydroxyzine and diphenhydramine are sedative antihistaminics. More sedative tricyclic antidepressants such as amitriptyline and doxepin are also promoted for the treatment of anxiety state. However, all these drugs also suppress the autonomic nervous system and can be called *sedative autonomic*. They do not modify muscle tone and are likely to cause adverse effects such as dryness of mouth, palpitation and confusion. None is superior to benzodiazepines.

BUSPIRONE : This is an azaspiro-decanedione anxiolytic agent, not related to benzodiazepines. Clinically, it is claimed to be as potent as diazepam or chlorazepate in its anxiolytic efficacy. However, it lacks the sedative-hypnotic, muscle relaxant and anticonvulsant properties of benzodiazepines. In therapeutic doses, it does not significantly alter reactive or coordinative skills. The drug appears to interact only with the dopaminergic system in a manner analogous to that of both dopamine agonist and antagonist. Experimentally, it does not interact significantly with CNS depressants and does not promote abuse or physical dependence. It is thus 'anxiolytic' in its action as compared to benzodiazepines. The drug causes less psychological impairment than diazepam.

Treatment of Neurosis : Anti-anxiety drugs

are mainly used in the treatment of anxiety states or neuroses. Neurosis is the commonest disorder in psychiatric practice. Neurotic reactions have been considered as the maladaptive results of conflict between unfulfilled desires and repressive tendencies. To some extent they are expressions of disappointments and frustrations in life.

The reactions and emotions of a patient suffering from anxiety state and neurosis are usually an exaggeration of those experienced by normal individuals in day to day life. Subjects generally complain of headache, tension, feeling of a tight band round the head, palpitation, tremulousness, dryness of mouth, hyperhidrosis, coldness of extremities, spasm of back muscle giving rise to vague bodyaches and insomnia. Such patients also suffer from bowel disturbances, phobias such as fear of dying, insanity and heart disease. Such fear complexes make them stop work. The appetite and libido, however, are not much affected and thoughts for committing suicide are absent unless it is associated with severe mental depression or major psychosis. The biochemical or neurophysiological basis of anxiety is uncertain and this makes the assessment of efficacy of drug therapy difficult. It is not surprising, therefore, that a wide range of drugs is claimed to be useful as anti-anxiety agents (Table 11.3). Antianxiety agents can reduce the somatic and autonomic disturbances which often dominate the picture and thus abolish physical malaise, bodyache and

Table 11.3 : Pharmacological properties of commonly used Antianxiety Drugs

	Phenobarbitone	Meprobamate	Benzodiazepines	Phenothiazines
Antianxiety/sedative ratio	+	++	++	±
Muscle relaxation	±	++	+++	-
Anticonvulsant action	+++	++	+++	-
Duration of action	+++	+	+++	++
Tolerance	++	+++	+	0
Habituation	±	+++	±	0
Physical dependence	++	+++	+	0
Disturbed sleep pattern	++	++	±	++
Liver microsomal enzyme induction	++	++	0	0
Potential suicide use	++	+++	0	0

0 = None, ± = Minimal, + = slight, ++ = Moderate, +++ = Great degree of probability. (Modified from Hollister L.E., Ann. Int. Med. 79:88, 1973)

anxiety. Long term studies with these drugs, however, indicate that none of the anti-anxiety agents produce permanent benefit which can come only from realization by the patient of the nature of his problems and his adjustment to them.

Some amount of anxiety is a normal physiological response that assists individuals in solving various problems in life. Indiscriminate use of anti-anxiety agents for prolonged periods is likely to kill all the initiative in the individual and make him permanently dependent on drugs. Effective treatment of neurosis needs the co-operation of the patient in facing his anxieties; and simple sharing of patient's problem by the physician can itself be therapeutic, although a complete solution of the problem may not always be possible. Thus, the vast majority of neurotics can be helped more by a sympathetic and understanding attitude of the doctor than by drugs. Drugs should be used only temporarily to lessen the patient's distress. This can be best achieved by using an anti-anxiety agent such as diazepam. Dosage schedule should be flexible and individualized. Since insomnia is a common complaint of these patients and as most anti-anxiety drugs induce sleep, the major dose might be given at bedtime with advantage. None of the drugs recommended is free from the dangers of drug dependence, though it is less severe with benzodiazepines. Benzodiazepines do not induce drug-metabolizing enzymes and produce remarkably little change in normal sleep patterns. Furthermore, benzodiazepines are considered safer than barbiturates when suicidal tendencies are suspected since suicidal attempts do not succeed even with massive overdosage of benzodiazepines. *Hence, barbiturates are better avoided on grounds of safety, relative lack of efficacy, drug abuse and dependence.*

Since anxiety is often episodic in intensity, drugs should be used to treat each episode and not be given continuously for prolonged periods. It must be emphasised that in anxious patients, placebo responses are frequent and definite. In some patients with severe anxiety, somatic symptoms such as palpitation, trembling and giddiness

dominate the clinical picture. In such cases, a beta-adrenergic blocking agent like propranolol may be useful.

In practice many patients complain of 'tension' with vague symptoms without any obvious signs of illness. These are due to minor maladjustments in day to day life and do not really need drug therapy. However, in the highly technical age that we live in, one always seeks for a technical solution to every problem. Unfortunately, such ideas are encouraged by drug firms and further enhanced by medical profession by publishing half-baked confusing reports on a condition which itself is difficult to evaluate. Drugs can temporarily modify the patient's emotional response to environmental factors. They are not expected to influence the environment or socio-economic situations. As pointed out, "It is required that we cope actively and almost constantly, with an outer environment and that we learn how to do this without disintegrating in new anxiety. To live is to be under tension, to be dissatisfied; to be anxious, sometimes unbearably so; to be angry, sometimes potently and impotently; to be everlastingly hungry; to some degree, for things that may be consciously well defined or very vague; to become depressed and discouraged; to become physically and psychosomatically ill; to worry obsessively and to become hysterically emotional. The range of normal functioning of mind is wide and flexible". Certainly, drugs should not be used every now and then to modify such normal cyclic behavioural changes without assessing the disability produced.

Severe anxiety, however, may be extremely disabling and often may be the presenting symptom of a more serious psychiatric disorder such as schizophrenia or depression. In such cases appropriate treatment of the underlying disorder is important, and benzodiazepines, in general, can be combined with antidepressants or antipsychotic drugs for this purpose. Further, acute attacks of anxiety, called panic reactions, do not respond to benzodiazepines; however, they respond well to a tricyclic antidepressant in small

doses (imipramine 25-50 mg/day); after the acute attack is over, a small dose of a benzodiazepine should be administered daily for 6-12 months.

ANTIDEPRESSANT DRUGS

Successful treatment of mental depression with drugs is one of the important advances in psychopharmacology in recent years. Several drugs are now available as 'antidepressants', sometimes also called as 'psychoanaleptics' or 'mood elevators'. These can be classified into:

I. Monoamine oxidase inhibitors (MAOI).

(i) *Hydrazine* MAOI, e.g. isocarboxazid, iproniazid and phenelzine.

(ii) *Nonhydrazine* MAOI e.g. tranylcypromine.

II. Cyclic compounds.

(a) *Monocyclic* : Tofenacin.

(b) *Bicyclic* : Viloxazine.

(c) *Tricyclic*: Imipramine, desipramine, amitriptyline, nortriptyline, doxepin and nitroazepine.

(d) *Tetracyclic* : Mianserin, maprotiline.

The tricyclic compounds are still the most preferred from this group.

III. Traizolopyridine derivative e.g. Trazodone.

IV. Lithium Carbonate.

V. Carbamazepine.

VI. Psychomotor stimulants: Caffeine, amphetamine, methylphenidate, pipradrol. These are not used in patients with affective disorders.

MONOAMINE OXIDASE INHIBITORS

This is a heterogeneous group of drugs which block the oxidative deamination of naturally occurring amines.

Pharmacological actions:

Behavioural effects : These drugs elevate the mood of depressed individuals. Such subjects feel more energetic, less sleepy and more fresh after antidepressant therapy. Tendency for suicidal rumination is markedly diminished. The

action is seen after a latent period of a few days to 3-4 weeks. In some cases agitation, talkativeness and restlessness may be precipitated.

Cardiovascular effects : These compounds do not exert any specific action on heart nor do they increase the coronary flow. The E.C.G. pattern in cases with angina pectoris is not altered. Some MAOI like pargyline exert a hypotensive effect and this drug has been used in the treatment of hypertension.

Reserpine reversal : Normally, animals treated with reserpine are inert, apathetic and do not take interest in the surroundings. In animals pretreated with MAOI, administration of reserpine produces agitation and excitement. This is known as 'reserpine reversal'. Reserpine reversal can be readily demonstrated in the rabbit or rat but is rarely observed in humans given therapeutic doses of MAOI.

Potentialiation of action of sympathomimetic amines : MAOI potentiate the sympathomimetic actions of other amines like amphetamine and ephedrine.

Miscellaneous : As these drugs also inhibit MAO and other enzymes present in liver, they prevent the metabolism of many drugs, thus prolonging their action. This may precipitate toxicity of these compounds. They are potent REM sleep inhibitors.

Mechanism of action : The enzyme MAO is present intracellularly in most of the tissues. The highest concentration is found in the liver. Its important function is to oxidise active biogenic amines like 5-hydroxytryptamine (5-HT), noradrenaline and dopamine to inactive compounds.

Relatively, there are large amounts of monoamines like 5-HT and noradrenaline concentrated in the hypothalamus and in other subcortical regions of the brain. These amines are normally stored in granules in the neurons and are liberated following nervous stimuli. The active amines thus liberated act on the receptors in the cells but do not accumulate as they are immediately metabolised by the enzyme MAO present in the brain. MAO inhibitors, by inhibiting this

enzyme, lead to accumulation of these amines in the brain, presumably both in free and stored forms. It has been demonstrated in animals that such an accumulation is associated with excitement and enhanced motor activity. Since MAOI are effective in the treatment of mental depression in man, it is believed that these drugs produce their pharmacological effects by increasing the brain levels of these active amines particularly the 5-HT. Tryptophan, the precursor of 5-HT and typtamine, taken orally, can potentiate the effect of MAOI.

Since reserpine is known to release 5-HT and noradrenaline from the brain sites, administration of MAOI prior to reserpine treatment leads to accumulation of these amines resulting into excitation instead of tranquillization, thus producing 'reserpine reversal'.

MAOI not only inhibit MAO but also inhibit to a certain extent other enzymes like histaminase. Further, they can also produce other pharmacological effects independent of MAO inhibition.

Given orally, these drugs exert a considerable effect on liver MAO enzymes because of their high concentration in portal circulation.

Absorption, fate and excretion : All these compounds are well absorbed on oral administration. They are probably metabolised quickly but they produce a long lasting effect on MAO enzymes. The information about their metabolism in man is inadequate, but the effect of MAOI continues for 10 to 14 days after the drug is withdrawn. This probably depends upon the time taken for enzyme regeneration.

Adverse reactions :

(a) **Behavioural effects :** These include headache, excitement and disturbed sleep. These drugs may activate latent psychosis and use of these drugs alone in cases of schizophrenia is contraindicated as this psychotic process is likely to be aggravated; in such circumstances they are combined with antipsychotic phenothiazines.

(b) **CNS Effects :** CNS stimulation as demonstrated by tremors, twitching, ataxia, hyper-reflexia, hyperthermia and even convulsions

may occur with these compounds. Drugs like iproniazid and isocarboxazid sometimes cause peripheral neuritis which responds to pyridoxine.

(c) **Hypertensive crisis :** This can be precipitated by concurrent administration of *sympathomimetic pressor amines* like amphetamine and ephedrine. Sudden rise in blood pressure may even cause subarachnoid haemorrhage. Hypertensive crisis can also occur in patients taking these drugs, if they eat cheese, which contains tyramine. Normally tyramine is metabolised in the liver by MAO enzymes. MAOI by inhibiting this detoxification lead to tyramine accumulation which is known to release noradrenaline from binding sites causing a marked rise in blood pressure. Eating of *broad beans* can also produce similar complication because of their content of dihydroxyphenylalanine (DOPA). *Yeast extract* contains both tyramine and histamine. Other foodstuffs which are incompatible with MAOI include *yoghurt, buttermilk, meat extracts, soyabeans, chocolates and banana peels*.

A hypertensive crisis should be treated with phentolamine (Regitine) 5 mg. I.V. administered slowly, while watching the blood pressure.

(d) **Autonomic effects :** Hydrazine compounds can cause constipation, dry mouth, blurring of vision, impotence and difficulty in micturition. They can also cause orthostatic hypotension.

(e) **Miscellaneous effects :** Hydrazine compounds, particularly iproniazid, cause hepatocellular jaundice. Allergic reactions are also known.

(f) **Adverse interaction with other drugs:** By blocking drug degradation, MAOI potentiate the action of numerous drugs like alcohol, barbiturates, morphine, pethidine, amphetamine, anaesthetics, antihistaminics, anticholinergic agents and tricyclic antidepressants. Thus, the normal dose of pethidine in a patient receiving MAOI can cause shock, collapse, respiratory depression and death. *The effects of adrenaline and noradrenaline, however, are not enhanced as they are inactivated by catechol-o-*

methyl transferase, another liver enzyme.

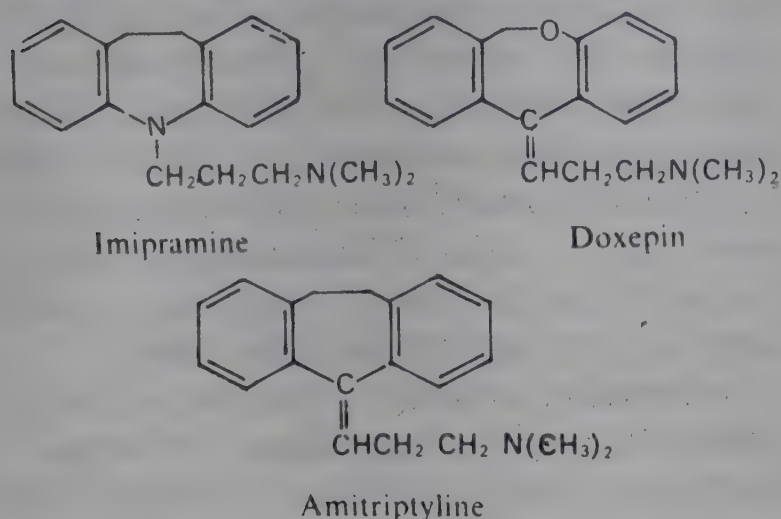


Fig. 11.3 :

(g) Acute toxic effects following overdose include agitation, hallucinations, hyper-pyrexia and convulsions. Blood pressure may be low or high. The treatment is mainly symptomatic. Drugs like vasopressor agents and barbiturates should be administered cautiously.

Preparations and dosages :

(i) Isocarboxazid (Marpan) - 10 mg. tablet, usual daily dose 10-30 mg. It may be increased upto 50 mg. daily.

(ii) Phenelzine sulfate (Nardil) - 15 mg. tablet. Usual daily dose 45-60 mg. Maximum daily dose recommended 75 mg.

Table 11.4: Cyclic antidepressant compounds

Compound	Sedative activity	Anti-cholinergic activity	Total daily dose mg	
			Out Patients	Hospital patients
Bicyclic Compounds				
Vilosazine	+	+	100-300	100-400
Tricyclic Compounds				
* Imipramine (Depsonil, Tofranil)	++	++	50-100	75-300
Desipramine (Norpramine)	+	+	50-100	75-300
Trimipramine (Surmontil)	+++	++	50-100	75-300
** Amitriptyline (Sarotena, Tryptanol)	+++	+++	50-100	75-300
Nartriptyline (Sensival)	++	+	20-60	40-100
Protriptyline (Vivactil)	+	++	15-40	15-60
Nitroxazepine (Sintamil)	++	+	50-150	75-200
Doxepin (Sinequan)	+++	+++	50-100	50-30
Tetracyclic Compounds				
Mianserine	+++	+	20-60	20-100
Trilazolopyridine Compounds				
Trazodone	+++	+	50-300	100-600

* Injections 25 mg in 2 ml for I.M. use.

** Injections 100 mg in 10 ml for I.M. use.

(iii) **Tranlycypromine (Parnate)** - 10 mg. tablet. Usual daily dose 10 - 30 mg. may be increased upto 50 mg.

With all these drugs smaller doses should be used for maintenance therapy and in old people.

TRICYCLIC COMPOUNDS

IMIPRAMINE, a dibenzazepine derivative, is the commonly employed tricyclic antidepressant drug at present and is discussed as a prototype. Structurally, it differs from phenothiazines in that the sulphur is replaced by an ethylene linkage. The other cyclic antidepressants are given in Table 11.4.

Pharmacological actions:

(a) **Behavioural effects** : Imipramine produces similar anti-depressant effect like MAOI, but the mode of action is different. The drug can reverse the depressant action of reserpine without restoring brain monoamines. It also has some anxiolytic action.

(b) **Central nervous system** : In animals, its CNS actions resemble those of antipsychotic phenothiazines. A single dose of 100 mg. in normal subjects causes drowsiness and a feeling of light headedness. Clinically, it produces some degree of sedation, enhances sleep and disrupts obsessive rumination. The drug suppresses REM sleep but increases stage 4 sleep.

It causes lowering of seizure threshold in animals and hence, should be prescribed with caution in patients with history of seizures.

Repeated administration of this drug in man causes sedation and may produce difficulty in concentration and thinking. Rarely, the drug may produce hallucinations. In therapeutic doses it does not affect the respiration. The drug has no euphoriant effect in normals, and psychic or physical dependence is rare.

(c) **Autonomic nervous system** : It can produce distinct anticholinergic actions such as dryness of mouth, constipation, blurred vision and palpitation. The drug has central as well as peripheral atropine-like effects.

(d) **Cardiovascular system** : Imipramine produces a fall in blood pressure in anaesthetised animals. Mild orthostatic hypotension is sometimes observed in man with therapeutic doses. Both imipramine and amitriptyline may cause inverted or flattened T wave, prolongation of QT interval and depressed ST segment in the E.C.G., even in therapeutic doses. With overdosage, these drugs can precipitate cardiac arrhythmias.

Mechanism of action : The mechanism by which the tricyclic antidepressants act in man is not known. It is known that all drugs which modify depression or mania have distinct effects on metabolism of noradrenaline (NA), dopamine (DA) and 5-HT. Normally a large proportion of NA liberated at the noradrenergic nerve endings is inactivated by reabsorption on to its storage sites. Tricyclic antidepressants inhibit the reuptake and cause a localised increase in active NA in the synaptic gap. They also cause blockade of pre-synaptic α_2 adrenoreceptors. Further, these compounds are also potent inhibitors of neuronal 5-HT uptake in the brain. However, it is not clear which of these effects is critical for the antidepressant action of these drugs if indeed this action does depend upon amine uptake inhibition. The tertiary amine derivatives, imipramine and amitriptyline are more potent inhibitors of 5-HT uptake than desipramine and nortriptyline; reverse is the situation with inhibition of NA uptake. Chloroimipramine is a potent inhibitor of 5-HT uptake. Normifensine, a tetrahydroisoquinoline compound, strongly inhibits the reuptake of DA and NA and is a weak inhibitor of 5-HT uptake; it causes little sedation. Thus, the same drugs often affect several neurotransmitter system (5-HT, noradrenaline, histamine and dopamine) to differing degrees. Further, they also possess strong central anticholinergic properties.

Absorption, fate and excretion : Imipramine is well absorbed when given orally; about 3 per cent is excreted in urine in the form of iminodibenzyl derivatives. In rabbits, the drug has been reported to get concentrated in the brain and the cardiac muscle, as compared to other body

tissues and fat. Imipramine is converted in the body to its metabolite desmethyylimipramine which is pharmacologically active. It has been suggested that the actions of imipramine are in fact actions produced by desmethyylimipramine. In general, the protein binding of tricyclic antidepressants is high (over 90%).

Adverse reactions:

(a) **Anticholinergic disturbances:** They constitute the commonest and the most troublesome adverse effects and no tricyclic compound is entirely free from them. These include dryness of mouth, difficulty in accommodation, tachycardia, difficulty in micturition, impotence, constipation, delayed ejaculation, and rarely hyperpyrexia. The drug should be used cautiously in patients with glaucoma or enlarged prostate. Rarely, it can cause paralytic ileus. Central anticholinergic effects are memory impairment, and in old persons, acute confusional episodes; these are not amenable to the peripheral cholinergic agonists.

(b) **Central nervous system:** Feeling of tiredness, lethargy, headache and drowsiness may be observed. Like MAOI these drugs can cause tremors, muscle jerking, ataxia and hyper-reflexia. Central anticholinergic action may cause confusion, disorientation or psychosis.

(c) **Cardiovascular system:** Tachycardia, cardiac arrhythmias and orthostatic hypotension can occur. Cardiomyopathy and heart failure have also been reported.

(d) **Allergic reactions** like urticaria, skin rashes, pruritus and photosensitivity.

(e) **Miscellaneous:** Like chlorpromazine, imipramine can cause cholestatic jaundice, agranulocytosis and edema. It should be used very cautiously in the presence of congestive cardiac failure. Unilateral or bilateral peroneal palsies have been reported following imipramine and amitriptyline. Tricyclic antidepressants cross the placental barrier and can affect the fetus.

(f) **Drug interactions:** Administered concurrently with MAOI, it can produce severe reactions resembling atropine poisoning leading to hyperpyrexia, convulsions and coma. Thyroid

preparations and phenothiazines may enhance its effects. Reversal of the hypotensive effect of guanethidine and mecamlamine has been observed. Imipramine potentiates the action of phenylephrine, adrenaline and noradrenaline and can cause fatal accidents.

Acute poisoning with this drug can produce hyperpyrexia, hypertension or hypotension, convulsions and coma. Cardiac complications may also be present. The treatment is symptomatic depending on particular effects manifested. Imipramine is a weak base and its urinary excretion can be enhanced by acidification of urine. Physostigmine salicylate, given parenterally, in the dose of 1-4 mg. every 1 hour, has been used successfully to treat anticholinergic CNS manifestations.

Preparations and dosage: See Table 11.4.

Therapeutic uses: (i) Treatment of depression: discussed later. (ii) Nocturnal enuresis: Imipramine, in a single bedtime dose of 10 to 75 mg., has been used with variable success in the treatment of enuresis.

Enuresis is defined as bedwetting that occurs after bladder control should have been achieved usually between the ages 2-3 years. The disorder exists in two forms: primary (persistent) and secondary (acquired or regressional). Primary enuresis is most common between the two types. The main treatment consists of bladder training and correction of psychopathologic factors.

Of the newer antidepressants, mianserin, a tetracyclic drug, produces fewer anticholinergic effects and is less cardiotoxic than the older drugs. It has a larger margin of safety than older drugs in patients with heart disease; the conventional antidepressants may be avoided in these situations. Similar claims are made for another new drug fluvoxamine (Faverin), which is highly selective for 5-H.T. system.

LITHIUM

LITHIUM CARBONATE: Lithium salts had been used for various purposes in past but were

given up because of toxicity. The use of lithium carbonate in mental illness was described by Cade in 1949 following the observation that it caused lethargy in guinea pigs.

The present evidence indicates that lithium is useful for terminating the manic episodes in patients with manic-depressive psychosis. It also seems to be useful in the prophylaxis of this condition. As compared to chlorpromazine, lithium is claimed to cause less drowsiness while controlling the marked psychomotor overactivity in the patients. The drug, however, does not exhibit positive activity in psycho-pharmacological screening in animals. The exact mechanism of action of lithium is not known. Lithium increases the rate of 5-HT synthesis in the brain. Further, the drug decreases the brain dopamine and noradrenaline synthesis and facilitates their neuronal reuptake; it may also modify the brain concentration of GABA.

Absorption, fate and excretion: Lithium carbonate is given orally. It is well absorbed and gets distributed throughout the total body water. The drug is mainly excreted in the urine, the renal clearance being proportional to its plasma concentration. Lithium decreases the sodium reabsorption by the renal tubules leading to sodium depletion. Patients on lithium treatment, therefore, should maintain adequate salt and water intake.

Adverse reactions : Lithium toxicity is closely related to its serum levels. Hence, the drug must be administered under supervision, preferably in a hospital with facilities for estimating serum lithium levels. Blood levels exceeding 2.0 mEq/l are associated with dangerous toxic effects.

Mild toxicity includes diarrhoea, vomiting, drowsiness, muscular weakness, tremors and ataxia. Cardiac arrhythmias can occur. It can also cause allergic reactions, blurred vision, glycosuria and polyuria. Large doses cause marked cerebellar disturbances, epileptiform seizures, hypotension and coma. Chronic administration may give rise to goitre formation, hypothyroidism

and abnormal E.C.G. changes. The drug should be administered very cautiously in the presence of cardiovascular, renal or brain damage.

Therapeutic uses : The principal use of lithium is to prevent recurrence of mania and of depressive episodes. It may also be used as a treatment for acute episodes of mania. The central features of the syndrome of mania are elevation of mood, increased activity and self important ideas. When mood is elevated, the patient appears cheerful and optimistic. Elation is interrupted by brief episodes of depression.

Maniac patients are overactive; sleep is reduced; speech is often rapid and copious. Appetite and sexual desire are increased. The patient believes that his ideas are brilliant and that his work is of outstanding quality. Sometimes, this is accompanied by grandiose delusions and occasionally by hallucinations. However, most patients can exert some control over their symptoms, at least for a short time.

Depressive and maniac symptoms sometimes occur at the same time. Patients who are overactive and talkative may be having profoundly depressive thoughts. Some maniac patients may become intensely depressed for a few hours and then return quickly to manic state.

The immediate treatment is usually with anti-psychotic drugs, and haloperidol is usually preferred. Chlorpromazine can also be used though it causes more sedation. After initial large doses (intramuscularly, if necessary), the patient is maintained on smaller doses depending upon the degree of overactivity. Once the patient is able to cooperate, kidney and thyroid function should be tested and lithium treatment started. Lithium carbonate is usually given initially in the dose of 600 mg thrice a day. The maintenance dose recommended is 300 - 400 mg twice a day. Lithium treatment should be used only in patients with normal sodium intake. As a prophylactic in maniac depressive psychosis, the drug is used in the dose of 600 - 1000 mg daily in two divided doses, 12 hours apart. It is to be noted that the drug

may take several months to achieve its full effect. It is usually continued for an year or longer and then gradually tapered off.

CARBAMAZEPINE: Carbamazepine is used as an alternative to lithium in the prophylaxis of maniac-depressive illness in patients who do not tolerate or do not respond to lithium. It seems particularly effective in patients who get frequent attacks (4 or more per year). It is generally used in the total daily dose of 400-600 mg, given in divided doses. For details of pharmacology see Chapter 7.

MISCELLANEOUS DRUGS

CAFFEINE and AMPHETAMINE : Although these drugs stimulate the central nervous system and can act as "psychic energizers", they are not true antidepressants. They increase energy, alertness and confidence in some patients. However, they do not correct the depressive state or prevent suicidal tendencies. In fact they may aggravate them. Amphetamine can produce drug dependence. It evokes release of noradrenaline and dopamine and blocks reuptake of these amines. (See Chapter 10 and 14).

PIPERIDYL DERIVATIVES: The drugs **pipradrol** (Meratran) and **methylphenidate** (Ritalin) have central stimulant actions like amphetamine. Their effects are intermediate between those of caffeine and amphetamine. These drugs, however, do not have peripheral sympathomimetic actions nor do they diminish appetite. Like caffeine they reduce fatigue and produce a feeling of well-being. These drugs, however, are more like analeptics and not true antidepressants. They are not useful in the treatment of severe depression and in large doses cause restlessness, insomnia, anxiety, tremors, palpitation, ataxia and even convulsions. Possibility of development of drug dependence is a major drawback of these drugs.

Methylphenidate has been used in the treatment of narcolepsy. Narcolepsy is a heritable neurologic disorder with varied manifestations

which begin to appear in late teens to twenties. The manifestations are (a) poor or disturbed sleep at night; (b) sudden, sleep attacks during any activity during day; (c) cataplexy: sudden onset of flaccid paralysis precipitated by anticipation, anger or surprise; (e) hypnagogic hallucinations: frightening hallucinations occurring at the onset of sleep; and (e) sleep paralysis: paralysis on awakening. The underlying biochemical abnormalities are believed to be (a) a widespread under-release of dopamine; and (b) a brainstem specific hyper response to acetylcholine. Sleep attacks respond to drugs which block central, dopamine re-uptake: methyl phenidate (10 mg 2-3 times a day) or dextroamphetamine (5-10 mg 3-4 times a day), the last dose being given by 4 PM in order to avoid interference with night sleep. Cataplexy responds to tricyclic antidepressants which suppress REM sleep: imipramine or desipramine (100 - 200 mg per day). Drugs from both groups should be titrated separately to achieve the best results for symptoms of sleep attacks and cataplexy. These drugs are discussed later.

Methylphenidate has been used in the treatment of children with attention deficit disorder. This condition is characterized by inattentiveness and impulsiveness with or without hyperactivity and impaired learning. These children are easily distracted and accident prone. C.N.S. stimulants like d-amphetamine, methylphenidate and pemo-line appear to have beneficial effects when given over a period of 1-3 months.

Treatment of depression:

Mental depression, like anxiety states, is a common psychiatric condition. It is, however, a more serious condition as it can disrupt the normal social life and may drive the individual to commit suicide. It is essential that this state is diagnosed early as antidepressant drugs can alleviate the majority of depressive illnesses. Furthermore, such effective treatment can now be given at home by the family doctor.

Although there is no unanimity regarding the clinical classification of depression, it can be broadly divided into two main groups. The first, 'reactive', 'neurotic' or 'psychological' depression,

is an exaggerated reaction to adversity manifested as gloom, unhappiness and tearfulness. It is precipitated by such factors as death in the family, sudden monetary loss, failure in examinations or accidents. The individual blames the situation rather than himself. The emotional feelings are intense. This type of depression responds favourably to moral, spiritual and social support from friends and relatives, who can share the problems and discuss the possibilities of solution. In many such 'situational crises', sedation produced by sedatives or antianxiety agents like benzodiazepines will be sufficient to tide over the crisis. The patient would show improvement with the change of situation.

The second group which is sometimes called 'endogenous' produces a varied picture. It usually occurs in the middle or later years of life. In its classical form an individual suffering from this type of depression shows retardation in thoughts, movement and speech; he remains withdrawn from the usual activities. The state is associated with early morning waking, occasional nightmares, feeling of guilt, anxiety and unworthiness or inferiority. There is a tendency for self blaming. These subjects generally complain of various aches and pains, tiredness, loss of appetite, loss of libido and subsequent loss of weight. There is a greater tendency to commit suicide in this group. Prompt use of antidepressant drugs and/or electro-convulsion therapy (ECT) produces dramatic results in many such cases. Endogenous depression appears to have biochemical basis in that it is probably closely related to decreased synthesis and turnover of brain 5-HT, noradrenaline and dopamine as well as an increased accumulation of acetylcholine; their relative importance is not clear. Patients who have attempted suicide had significantly lower C.S.F. levels of 5-H.T. metabolite, 5-Hydroxy indolacetic acid (H.I.A.A.) than those who had not.

For the successful treatment of depression, doctor-patient relationship is important. One must try to create confidence in such patients and make them feel that they have at last met someone who can do something for them. Nothing should

be done to increase their guilt feeling.

It is worth searching for possible external factors contributing to the depressive illness and to try to reduce their impact by modifying the environment or by some form of psychotherapy.

From the various antidepressant drugs now available it is better to be familiar with one or two drugs rather than go for the unfamiliar 'latest' in the market. None of the newer antidepressants appear to be consistently therapeutically superior to imipramine or amitriptyline. Considering their secondary psychotropic effects, amitriptyline, doxepin and dothiepin are more sedative than imipramine whereas nortriptyline, desipramine and protriptyline have negligible sedative action. In fact, some of these may act as stimulants. Hence, patients with agitation or anxiety are best treated with a sedative antidepressant. Treatment with amitriptyline is often associated with substantial weight gain and should be used when this is desired. Imipramine is perhaps the most suitable preparation for general purpose. To begin with, it is generally administered in a dose of 25 mg. thrice daily and then increased to 50 mg. and 75 mg. thrice daily during second and third week respectively depending upon the individual response. Smaller doses are employed in old people. Because of pharmacokinetic considerations, the entire daily dose of imipramine and amitriptyline may be given at bedtime. When these drugs are given at bedtime, their sedative effect may eliminate the need for an additional hypnotic drug. However, some adverse effects may be more marked in some patients taking single large doses. No response occurs below a certain, critical drug concentration. Wide variations are known to occur in the serum concentration in different people on the same dose. The elderly metabolise tricyclic antidepressants more slowly and may achieve therapeutic plasma concentrations with a dose as low as 25 - 50 mg daily. Drugs like amitriptyline and desipramine produce similar response as imipramine, perhaps a little more quickly. Patterns of dosage may vary considerably depending upon the drug selected. There is also a considerable variation in the dose

requirement among patients. Once a therapeutic dose has been established, the entire daily dose may be given at night. In majority of cases recovery occurs within 4-8 weeks, but the treatment should be continued for 4-6 months. Although the list of adverse effects is formidable, the incidence is not very high and these effects usually occur during the first few days of treatment. Anticholinergic adverse effects are the most common and are annoying, particularly in the elderly subjects. If improvement does not occur after 3-4 weeks of therapy, continuation of drugs or further increase of dosage is unlikely to bring about further improvement. In such cases an antidepressant belonging to another group is indicated. Patients requiring long term antidepressant therapy can be maintained on lower dosage schedules, the correct dose level being determined by trial and error. Since antidepressants produce only a symptomatic relief, maintenance dose for several weeks or months may be necessary.

MAO inhibitors are clinically less effective and potentially more dangerous and should be used only if tricyclic drugs fail to improve the condition. Although it is claimed that younger patients do better with MAO inhibitors, these compounds cannot be recommended as drugs of choice. Combination of imipramine group with MAO inhibitors is hazardous and can cause agitation, convulsions, coma and death.

Anti-anxiety agents like meprobamate and benzodiazepines may be combined to lessen anxiety in early stages while a sedative like diazepam and flurazepam may be given at bedtime in those who complain of early waking. Phenothiazines can be combined with tricyclic compounds in depression with accompanying agitation or psychotic symptoms.

It may be pointed out that the relationship between depression and anxiety is complex. Both these can coexist in a patient with neurotic illness, in schizophrenia or in organic syndromes. Finally, depression can be precipitated as a reaction to severe anxiety.

In severe cases with delusions, suicidal ruminations, marked retardation or severe agitation,

ECT is preferred to drug therapy, as the beneficial results can be obtained more quickly. A history of suicidal attempt or strong suicidal thoughts points to the need for immediate hospitalization.

Although the drugs and other treatment can now achieve remarkable therapeutic results, the prophylactic effect of kindness from relatives and friends could be immense and the patient should be made to feel that he is useful to the family and community and not an unwanted, useless burden. Lastly, it must be realised that mild depressions are normal manifestations of cyclic variations in mood, and antidepressant drugs which are potentially toxic agents, should not be used indiscriminately as euphorants in such cases.

Psychotherapeutic drug combinations:

Psychotherapeutic agents possess varied pharmacological actions and their combinations can produce dangerous drug interactions. Unfortunately, polypharmacy is widely prevalent and the number of combinations prescribed in practice is amazing. To quote Hollister "A single hospitalized psychotic patient often is given two phenothiazines (based on the unproved contention that a combination provides full therapeutic effects but only fractional side effects), a tricyclic antidepressant (presumably because the patient may seem withdrawn or depressed), an anticholinergic antiparkinsonian drug (most often gratuitously, either in the absence of any overt Parkinson's syndrome or without awareness that the anticholinergic action of the tricyclic protects against extrapyramidal effects), a hypnotic, such as chloral hydrate (for sleep), and a stimulant, as dextroamphetamine (to start the next day). Aside from the possibility that opposing effects may attenuate the desired therapeutic action, the greatest danger is that the accumulation of anticholinergic effects from the phenothiazines, the tricyclic, and the antiparkinsonian agent may produce bladder or bowel paralysis or may precipitate an attack of glaucoma. The fact that many patients improve mentally when all such drugs are withdrawn may indicate that they were suffering from mental confusion associated with overdoses of centrally acting anticholinergic drugs." It must be

emphasized therefore that the combinations should be prescribed only when they are a must and then strict vigilance maintained for possible drug interactions.

PSYCHOTOGENIC DRUGS

These are the drugs which are capable of producing psychosis---"a state characterised by maladaptive behaviour in which an individual reacts inappropriately to his environment." These drugs produce depersonalization, changes in mood and a variety of effects on memory and learned behaviour. As some of these effects resemble certain manifestations observed in natural psychosis such as schizophrenia, these drugs are also called as 'psychotomimetic'; and because of their ability to produce hallucinations they are sometimes designated as 'hallucinogenic drugs' or 'hallucinogens'.

Toxic psychosis is known to occur following toxic doses of many pharmacological agents; but these are associated with other organic and neurological disturbances such as delirium, nystagmus and disturbances of equilibrium, speech and gait. Psychotogenic drugs, however, can produce psychotic states selectively, without delirium and neurological disturbances. The important psychotogenic drugs can be classified chemically as (i) those with indol ring (indolic) such as lysergic acid diethylamide, psilocybine, and bufotenine, and (ii) those without indol ring (non-indolic) such as mescaline and *Cannabis indica*.

LYSERGIC ACID DIETHYLAMIDE: LSD is an amine alkaloid, synthesized from ergot by Stoll and Hopmann in 1938. It has some resemblance to ergometrine and possesses oxytocic action. Its central actions were recognised accidentally by Hopmann in 1943.

Pharmacological actions : The drug is rapidly absorbed on oral administration and can produce its actions in doses as low as 20-25 μ g. in susceptible individuals. Generally, LSD has a disintegrating effect on both inborn and learned behaviour patterns. Animal behaviour under LSD

is known to be disorganized. Thus, under its influence the garden spider produces a defective web and a fish becomes disoriented. Individuals under LSD effect exhibit marked changes in mood with emotional outbursts and they may laugh or cry on slightest provocation. It produces a blocking effect on the performance in various tests designed for evaluation and judgement. Motivation is impaired and procedures like writing or drawing become disintegrated and ultimately impossible. Many subjects experience a fear of disintegration of the self. The syndrome clears up after about 12 hours.

Associated with these behavioural changes certain sympathomimetic actions such as dilatation of pupil, tachycardia, tremor, piloerection and hyperglycemia have also been observed in man. These autonomic effects are probably of central origin. The drug sometimes causes nausea and frequency of micturition without diuresis.

Tolerance to behavioural effects of LSD is known to develop both in man and monkeys and a cross tolerance exists between LSD, mescaline and psilocybine. The drug causes psychic dependence. After a certain drug-free interval, the tolerance may disappear.

Mechanism of action : LSD blocks the peripheral actions of 5-HT. However, there is no correlation between this peripheral blocking activity and the central psychotogenic effects. Furthermore, 2-bromo LSD and methysergide, both powerful antagonists of 5-HT produce negligible psychotomimetic effects. Various theories have been postulated to explain the central actions of LSD but the exact site and the mode of action remain still obscure. Human studies on the metabolism of LSD are incomplete but the drug is metabolised probably to certain active metabolites in the liver.

Adverse reactions : These vary markedly from species to species. In animals, death is due to respiratory failure. In man, the margin of safety between effective dose and lethal dose appears to be wide. Sometimes, it produces suicidal tendencies. Although the psychotic changes produced by LSD are generally reversible, the drug is capable

of producing permanent psychosis and personality changes in some individuals; this is the greatest danger involved in the therapeutic application of LSD. The drug is also claimed to produce chromosomal damage.

Phenothiazines such as chlorpromazine can antagonise many acute effects of LSD while reserpine is known to potentiate its actions.

Uses : The drug is used as a research tool to produce experimental psychosis.

Other agents chemically related to LSD such as psilocybine, 5-hydroxy-dimethyl tryptamine (bufotenine) and harmine produce similar psychotogenic actions. They are not used therapeutically.

MESCALINE: The alkaloid mescaline was isolated in 1846 from the cactus *Lophophora williamsii*. Its chemical structure was elucidated in 1918. The Red Indian tribes in Mexico and in North America were using this cactus as an intoxicant to produce ecstatic states on special religious occasions.

Pharmacological actions : Given orally the drug produces anxiety, tremors, sympathomimetic effects and hallucinations. Individuals under the effect of mescaline get visual hallucinations of fantastic and brilliantly coloured figures, animals and people. The subject may get the feeling of floating in space with ever increasing feeling of dissolution. It is no wonder that the Red Indians believed that God put some of His Holy Spirit into the plant! Beside such colourful hallucinations the drug also produces delusions, depersonalization, disturbances of thought, excitement, restlessness, and intellectual and mood changes.

To produce its effects the drug has to be taken in dose of 500 mg. and the effects of a single dose persist for about 12 hours. Tolerance to mescaline is known but drug dependence is doubtful.

Uses : It has been employed as an experimental tool to produce model psychosis in the study of psychotic disorders.

CANNABIS (MARIHUANA) : Cannabis is one of the oldest herbal remedies, known since

3000 B.C. It is obtained from the hemp plants, *Cannabis sativa* and *Cannabis indica*. The active ingredient is present in the resinous exudate of the tops of the female plant. The resin is known as *Hashish* or *Charas*. *Bhang* is prepared from the dried leaves and the flowering shoots while *ganja* is the resinous mass obtained from the small leaves and brackets of inflorescence. The term *Marihuana* is used to describe any plant part or extract containing the active principle.

The active principle of Cannabis is known as tetrahydrocannabinol; synthetic derivatives of this have also been prepared and studied.

Pharmacological actions :

(a) **Acute effects :** These have been studied in man following the administration of the major component of cannabis, synthetic trans-delta-9-tetrahydrocannabinol (THC). When smoked, THC is rapidly absorbed and effects appear within minutes and last for about 2-3 hours. Given orally, the onset of action is delayed upto 30 minutes-2 hours. The pulse rate increases, conjunctiva becomes red and blood pressure may fall slightly; at higher doses, orthostatic hypotension occurs. Muscle strength is decreased; appetite is inconsistently increased, leading to increase in food intake.

The drug produces varying degree of CNS and behavioural effects. There is an initial period of euphoria or "high", which is followed by drowsiness. It produces a dreamy state, feeling of well being, excitement and inner joyousness. An individual under the influence of cannabis may become garrulous and hilarious, exhibiting sometimes uncontrollable laughter even with minimal stimuli. Violent or aggressive behaviour, however, is rare. Time sense is altered and hearing becomes less discriminating. Vision becomes apparently sharper with many visual distortions. The drug causes depersonalization and difficulty in concentrating and thinking. Similar symptoms are produced by many other psychotomimetics. The subjective effects depend on the dose, the route of administration and the personality of the individual. Sometimes, the drug causes nausea,

vomiting, increased urinary frequency and dryness of mouth.

(b) Chronic effects : The effects of chronic use are somewhat less certain. Some degree of tolerance is known to develop rapidly and a mild withdrawal reaction may occur; this is, however, not associated with craving or physical dependence. Some of the acute effects may be reversed; thus a slow heart rate is observed instead of increased rate as seen following acute use. Heavy chronic cannabis users can develop an amotivated syndrome, with apathy and loss of academic performance in students. Since cannabis is concentrated in the limbic system, the motivational centre in the brain, and interferes with memory, cognition and psychomotor performance, such an effect is expected. Even social doses seriously impair car driving ability because of distortions of time and space estimations, reduced vigilance and incoordination and effects persist for many hours because the drug is eliminated slowly. Interestingly, the drug was found to lower intraocular pressure in some individuals.

Adverse reactions : Large doses of cannabis may cause an acute panic reaction, a toxic delirium, an acute paranoid state or acute mania. However, the existence of a specific cannabis psychosis, as postulated earlier, is not established. It seems likely that psychopathology may predispose to cannabis use rather than the other way round.

Acute panic state is perhaps the most common psychic reaction and is characterized by anxiety, confusion and other unpleasant experiences. Occasionally it may cause a dissociative reaction, and depersonalization which may be long lasting.

Very large doses of cannabis may cause toxic delirium characterized by marked memory impairment, confusion and disorientation. Similar reactions are seen with many other drugs e.g. *Datura stramonium*.

A self limiting hypomanic-schizophrenic-like psychosis following marijuana has been documented. However, evidence for a specific type of psychosis associated with its chronic use is still

elusive. Cannabis probably unmasks latent psychiatric disorders and that action probably accounts for the great variety of psychiatric reactions which have been described following its use. The drug can aggravate schizophrenia in patients controlled on neuroleptics.

Sometimes, the drug may produce "flashback" reactions in which events associated with drug use are suddenly thrust into consciousness in the non-drugged state. This phenomenon is most common with LSD and other hallucinogens, and may occur many months after the last use of such drugs. In case of cannabis, the reaction is mild.

Tolerance has now been shown for most of the actions of THC. It develops at varying rates for different actions but it is rapidly reversible. Large doses of THC are required over a long period for tolerance to develop. Cross-tolerance between THC and morphine has been shown in rats but not to mescaline or LSD.

Chronic cannabis users may have decreased sperm production. Women may have anovulatory menstrual cycles associated with decreased LH. The drug may cause deterioration of glucose tolerance and aggravation of diabetes mellitus, and may inhibit 'T' cell function.

Chronic cannabis smokers, like tobacco smokers, can develop significant airway obstruction, bronchitis, cough and precancerous mucosal changes.

Therapeutic uses : Although cannabis possesses antiemetic, mild analgesic, muscle relaxant, anticonvulsant and sedative-hypnotic actions, it cannot be recommended for these purposes because of its other actions and the availability of safer and specific drugs for treating such cases.

Marijuana is now firmly established as another social drug in the highly developed countries.

A new synthetic cannabinoid, **nabilone**, has been shown to possess antiemetic properties and the drug was considered superior to prochlorperazine as an antiemetic, in patients receiving cancer chemotherapy.

DRUGS INDUCED PSYCHIATRIC SYNDROMES

Psychiatric disturbances are often attributed to concomitantly administered drugs; yet, it is generally difficult to establish the causal relationship between the two. Such a drug induced reaction should, however, be suspected whenever an unexpected psychiatric disturbance arises suddenly in a person of good previous personality, after a new drug of any type has been taken. The suspected medication should be discontinued, if possible. The psychiatric reactions to drugs can be broadly categorized into the following types.

(1) **Delirium** (acute brain syndrome, toxic confusional state): This is characterized by a fluctuating clouding of consciousness, restlessness, emotional changes usually of fear and perplexity and, in severe cases, paranoid delusions or visual hallucinations. The elderly are particularly susceptible to such reactions. They may follow overdose or drug withdrawal, or may be due to intolerance to a normal therapeutic dose. Although any drug can cause such states, CNS depressants (including alcohol), anticholinergics, betablockers and cimetidine are the ones implicated most frequently.

(2) **Psychotic states**: Hallucinogens such as LSD can induce a psychotic state with clear consciousness, paranoid delusions and visual hallucinations. States closely resembling schizophrenia with auditory hallucinations, thought disorder, aggressive behaviour and occasionally violence and suicide are seen with the CNS stimulants (cocaine and amphetamine), sympathomimetic nasal sprays, anorexiant and beta adrenergic agonists. Other drugs which cause psychotic states are beta-adrenergic blockers, opioids, dopamine agonists, glucocorticoids and rarely NSAID.

(3) **Manic states** are seen with antidepressants, anticholinergics, high doses of corticosteroids, isoniazid, levodopa, dexamphetamine and clonidine.

(4) **Depression** has been reported with antihypertensive drugs (reserpine, methyldopa, clonidine, propranolol and pindolol), levodopa, anti-convulsants, cimetidine and (withdrawal of) fenfluramine.

(5) **Behaviour disorders** that have been reported are withdrawal syndrome after cessation of benzodiazepines and akathisia during treatment with neuroleptic drugs.

DRUGS AND MEMORY

In recent years, attempts have been made to develop new drugs for improving memory in the treatment of cognitive deterioration such as that observed in Alzheimer's disease. Alzheimer's disease is a steadily progressive, neuropsychiatric condition that is mainly characterized by memory deficit and debility. Although its cause is not known, some specific anatomical and neurochemical lesions have been observed in patients suffering from this disease. There appears to be a deficiency of choline acetyltransferase, an enzyme responsible for the formation of acetylcholine from choline and acetyl coenzyme A. A selective loss of cholinergic neurons in the septal diagonal band of the Broca's nucleus basalis system has been demonstrated in patients with Alzheimer's dementia. Various vasodilators and metabolic enhancers (Nootropics) have been used in this condition with doubtful results. Tetrahydroaminoacridine is a potent, centrally acting, anticholinergic drug, which has been recently tried in Alzheimer's disease with equivocal results. The drug is under trial.

Section III : Local Anaesthetics

12 Cocaine, Procaine and other Synthetic Local Anaesthetics

Local anaesthetics are drugs which, when applied directly to peripheral nervous tissue, block nerve conduction and abolish all sensations in the part supplied by the nerve. They are generally applied to somatic nerves and are capable of acting on axons, cell body, dendrites and synapses.

Local anaesthetics are divided into following groups:

I. Natural : Cocaine.

II. Synthetic nitrogenous compounds:

(a) Derivatives of para-amino-benzoic acid.

(i) Freely soluble : procaine, amethocaine.

(ii) Poorly soluble : benzocaine, orthocaine.

(b) Derivatives of acetanilide e.g. lignocaine (lidocaine).

(c) Quinoline derivatives e.g. cinchocaine (nupercaine).

III. Synthetic non-nitrogenous compounds : Benzyl alcohol, propanediol.

IV. Miscellaneous drugs with local action : Clove oil, phenol, chlorpromazine, certain antihistaminics e.g. diphenhydramine. There are discussed elsewhere.

Local anaesthesia can also be produced by physical methods such as refrigeration, using various procedures such as application of ice and ethyl chloride spray.

General properties of local anaesthetics:

Synthetic local anaesthetic drugs have many properties in common. They possess varying degrees of water and lipoidal solubility; since the nervous tissue is rich in lipid, lipoidal solubility is

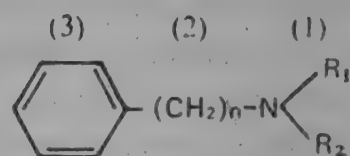
essential for migration of the drug into the neuronal fibre, while water solubility helps to get the drug to the site of action from the site of injection or application. Thus, the local anaesthetic with high lipid solubility but low water solubility will not be much useful because of difficulty in transportation through the aqueous phase surrounding the neuronal fibre. All the useful local anaesthetics consist of three parts:

(1) hydrophilic amino group

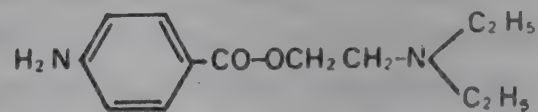
(2) intermediate chain

(3) lipophilic aromatic group

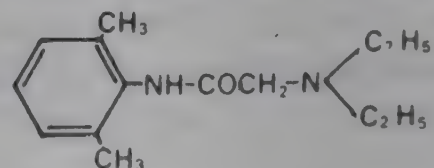
The fundamental structure may be represented by



Basic structure



Procaine



Lignocaine

Fig. 12.1
Basic structure of local anaesthetics
Procaine and Lignocaine

Due to presence of amino nitrogen, these drugs are bases and form soluble salt with acids (pH 4.6). In the tissues where the pH is alkaline (pH 7.4), the free base is liberated and produces its pharmacological action on the tissues. They are thus dispensed as water soluble salts, generally as hydrochlorides.

Majority of the clinically useful local anaesthetics are nitrogen containing compounds either in the form of esters e.g. procaine, or amides e.g. lidocaine and cinchocaines; their generic name ends with suffix 'caine'. Non-nitrogenous compounds with local anaesthetic properties like benzyl alcohol have their generic names ending with suffix 'ol', e.g. propanediol, cyclohexanol; these compounds, however, are not so useful.

Mechanism of action: Local anaesthetics block both the generation and the conduction of the nerve impulse. The blockade probably results from the biochemical changes caused by the drug on the lipotropic film of the cell membrane. It is suggested that the local anaesthetics like procaine prevent the increase in permeability of the cell membrane to Na^+ ion, which is the first event in depolarization. Thus, an action potential is not generated. This action affecting the process of depolarization, leading to failure of propagation of an impulse without affecting the resting potential, is known as '*membrane stabilizing effect*'. Calcium is also involved in the action of local anaesthetics on nerve and muscle. As in the case of general anaesthetics, there is no correlation between the distribution coefficient and the anaesthetic potency.

A smaller nerve fibre presents a greater surface area per unit volume for the action of an anaesthetic than a larger fibre. Smaller fibres are, therefore, blocked first. Thus, autonomic fibres are blocked first, followed by sensory fibres conducting temperature and pain and then those transmitting touch, pressure and vibration sensations. Motor fibres are attacked last. The recovery of function appears to occur in the reverse order.

Local anaesthetics are less effective when in-

jected into an inflamed area. The exact cause for this phenomenon is not known.

Pharmacological actions : Besides the local anaesthetic properties, cocaine and the other nitrogenous synthetic substitutes have important actions on other systems.

(a) **Central nervous system:** Commonly they cause light headedness, dizziness and blurred vision. The C.N.S. is stimulated, producing restlessness, tremors and in toxic doses, convulsions. Central stimulation is followed by depression, and death is usually due to respiratory depression.

Cocaine in smaller doses acts more prominently on the higher centres causing euphoria, mental alertness and hallucinations.

(b) **Cardiovascular system :** These drugs are myocardiac depressants. The heart rate and the amplitude of contraction are decreased, the excitability threshold and the refractory period are increased while conduction is slowed. Higher concentrations produce change in the E.C.G. and sometimes precipitate ventricular fibrillation or cardiac standstill in diastole. Procainamide (related to procaine) and lignocaine are used therapeutically for their cardiac depressant properties.

Excepting cocaine, which is rarely used therapeutically, all the other drugs produce hypotension, probably by a direct action on the vessel wall; this property is related to their neuron blocking potency. Cocaine has a vasoconstrictor action.

(c) **Other actions :** Nitrogenous synthetic local anaesthetics have direct spasmolytic action on smooth muscle and in large doses, they can produce neuromuscular blockade.

Absorption, fate and excretion : Local anaesthetics are not absorbed from unbroken skin. Applied to the mucous membrane, the absorption varies with the mucous surface. Thus, absorption is more rapid from the trachea than from the pharynx while it is poor through the urinary bladder. A considerable amount of drug can get absorbed from a raw granulating surface.

When used by infiltration, the absorption can be retarded by using vasoconstrictor agents like

adrenaline along with the drug. It must be emphasized that a latent period of several minutes elapses between drug application and therapeutic effect. Failure to allow sufficient time for establishment of block may convey the erroneous impression that the dose employed is inadequate; this leads to use of unnecessarily large doses which may prove toxic and even fatal.

Many of the common local anaesthetics are esters and are metabolized by hydrolysis which occurs in both liver and plasma. The amide-like local anaesthetics such as lignocaine are degraded by liver microsomes. There is a species variation; thus, cocaine is largely detoxified in rabbits while it is excreted unchanged in human urine. Little is known about the degradation of the drug in nerves. Slowly and incompletely detoxified drugs would obviously produce greater systemic toxicity, if absorbed.

Local anaesthetics such as procaine, containing P.A.B.A. as a component considerably decrease the clinical effectiveness of sulfonamides. Anticholinesterases increase the duration of action of procaine by inhibiting its destruction by plasma pseudocholinesterase.

Adverse reactions:

(a) *Intolerance* : This may manifest as a mild allergic dermatitis, a typical asthmatic attack or a severe fatal anaphylactic reaction. It is generally seen with the local anaesthetics of the ester type and may show cross sensitivity with chemically related compounds. Intradermal sensitivity test is advocated before using these drugs. A negative response, however, does not rule out drug sensitivity.

(b) *C.V.S.* : Fall of blood pressure and cardiac arrest can sometimes occur. Hypotension should be treated with vasoconstrictor drugs like noradrenaline and ephedrine. If the heart stops, rhythmic compression of sternum to give external cardiac massage or, if necessary, thoracotomy is indicated. During emergency, mouth to mouth breathing keeps the air-way patent.

(c) *C.N.S.* : This toxicity can be countered to a certain extent by preanaesthetic administration of

diazepam. If convulsions occur, diazepam or a short acting barbiturate, preferably sodium pentothal, is given intravenously. Oxygen is given to prevent hypoxia; artificial ventilation is necessary in the presence of respiratory arrest.

Barbiturates are only useful for controlling convulsions. In the presence of medullary depression, actions of local anaesthetics and barbiturates are additive and this can be dangerous.

Factors which determine the toxicity are :

- (1) The rate of absorption, diffusion and inactivation of the drug,
- (2) individual susceptibility and
- (3) inherent toxicity of the drug.

Prevention of toxicity :

- (a) Enquire about the history of allergy.
- (b) Drugs should be given cautiously in the presence of liver and myocardial damage.
- (c) Avoid food at least 4 hours prior to anaesthesia to prevent vomiting. Preanaesthetically phenobarbitone may be given.
- (d) Select the proper site; correct knowledge of the nerve course is needed before attempting a nerve block.
- (e) Use minimal effective dose, well diluted, preferably with the vasoconstrictor drug, adrenaline. Avoid intravenous injection.
- (f) Wait after injection; remember the latent period.
- (g) Observe the face for any twitching, excitement, and pulse for tachycardia, if any.
- (h) Observe post-operatively for allergic reactions; warn the patient against using the drug again, if allergy is observed.

Therapeutic uses:

(i) *Surface anaesthesia* : The insoluble compounds are generally used as ointment to relieve pain due to ulcers and fissures. A 2-4 per cent lignocaine or 1 per cent amethocaine solution is used in ophthalmologic and otorhinolaryngologic surgical practice as drops or spray because of its penetrating power. Procaine is unsuitable for this purpose as it has poor penetrating power. A poorly soluble drug as benzocaine, is sometimes used in lozenges or dusting powders.

(ii) *Infiltration anaesthesia* : In this proce-

sure the nerve endings are anaesthetised by their direct exposure to the drug. The drug is infiltrated subcutaneously. Procaine 2 per cent and lignocaine 2 per cent are most commonly used. They are mixed with adrenaline 1:200,000 to 250,000 to prolong the action. Lignocaine acts longer than procaine, but procaine is cheaper and more easily available. Adrenaline should be avoided when local anaesthetics are used to produce ring block to anaesthetize the digits or penis, in order to avoid local ischaemia and in patients with known myocardial disease.

(iii) **Nerve block or conduction block** where the drug is injected very close to the nerve e.g. brachial plexus.

(iv) **Spinal anaesthesia:** In this procedure the drug is injected into the subarachnoid space. Its level in the space is adjusted by using solutions with higher (hyperbaric) or lower (hypobaric) specific gravity than that of C.S.F., as vehicles.

Usually, the injection is made 'heavy' by adding dextrose or 'light' (approximately isotonic) by adding saline. The position of the patient is also important in limiting the block to the desired level. Procaine and lignocaine are the most commonly used drugs.

Due to sympathetic blockade these drugs produce arteriolar dilatation, decreased venous tone, post-arteriolar pooling of blood and diminished venous return to the heart. The cardiac output is reduced and the blood pressure falls. This is one of the most important complications of spinal anaesthesia. The arterial hypotension can be treated by:

(a) Elevation of the legs or wrapping the legs in elastic bandages to increase venous return.

(b) Rapid intravenous infusion of fluids for filling the dilated vascular bed.

(c) Use of vasopressor drugs e.g. ephedrine and methoxamine to restore arteriolar and venous

Table 12.1: Concentrations and maximum dosage of commonly used local anaesthetics

Drug	Topical use	Injections	Dose mg.
Procaine hydrochloride (Novocaine)	Ineffective	Infiltration 1-2% (200 ml) Nerve block 1-2% Spinal 10%	1000 600-900 80-200
Amethocaine hydrochloride (Pontocaine)	Eye drops 0.25-1% Respiratory tract 1-2%	Not recommended	
Lidocaine hydrochloride (Xylocaine)	Surface anaesthesia 1-2% Respiratory tract 2-4% Ointment 5%	Infiltration 0.5% Nerve block 1-2% Spinal 5%	250-400 250-400 25 - 75
Bupivacaine (Marcaine)		Local 0.25% infiltration Dental 0.5% Spinal 0.75%	50-100 9-18 7.5-11.25
Benzocaine (insoluble)	Dusting powder 2-10% Throat lozenges Ointment 5%	—	—

tone.

When used as spinal anaesthetics, lignocaine and other related compounds give good muscle relaxation and allow the use of cautery and electrical appliances during surgery. These drugs, however, are not suitable for surgery above the diaphragm and in apprehensive and mentally disturbed patients. Failure to block the vagus may precipitate hypotension and hiccough due to reflex stimulation during abdominal surgery. Headache, which is commonly observed following spinal anaesthesia, is probably due to leakage of cerebrospinal fluid from site of puncture and it responds to analgesic drugs.

Other complications include post-operative urinary retention and intestinal atony. Treatment of these is discussed in Chapter 15.

(v) **Systemic uses:**

(a) In the treatment of cardiac arrhythmias (See Chapter 25).

(b) As intravenous analgesics in the treatment of severe pruritus and pain due to malignancy; they are not very useful for this purpose.

COCAINE is an alkaloid obtained from the leaves of the coca tree (*Erythroxylon coca*) and other species. It is the methylbenzoyl ester of ecgonine which is chemically closely related to atropine.

Pharmacological actions :

Apart from its local anaesthetic action, it exerts a stimulant action on the central nervous system. It acts on the autonomic centres and the cerebrum. It potentiates the actions of adrenaline. It produces euphoria and abolishes the sense of fatigue and hunger. It is a drug of addiction. Cocaine addicts show paranoid and homicidal tendencies.

The effect of cocaine on dopaminergic neuronal systems may be involved in producing euphoria and addiction. In the short term, cocaine appears to stimulate dopaminergic neurotransmission by blocking the re-uptake of dopamine. With long term use the nerve terminals may become depleted of dopamine. The euphoric effect of cocaine, consumed by smoking lasts for

20 minutes while that following intranasal administration may last for 1 - 1½ hours.

Cocaine blocks the presynaptic re-uptake of the neurotransmitters norepinephrine and dopamine, producing an excess of neurotransmitter at the post-synaptic receptor sites. Activation of sympathetic nervous system produces vasoconstriction, an acute rise in B.P., tachycardia and a predisposition to ventricular arrhythmias and convulsions. It may also result in mydriasis, hyperglycemia and hyperthermia.

The concentration used to produce local anaesthesia is poisonous to many structures like leucocytes and tissue cells. It is a protoplasmic poison.

Adverse reactions :

Cocaine can cause life threatening arrhythmias and acute myocardial infarction.

At low doses, cocaine can delay ejaculation and orgasm and cause elevation and heightened sensory awareness. On the other hand, in chronic users it may cause sexual dysfunction and sexual disinterest. It is, therefore, not a true aphrodisiac.

Deaths have been reported following cocaine administration by all routes. Since it is metabolised by plasma and liver cholinesterases, people with deficiency of these enzymes (liver disease), infants, pregnant women and old people are at greater risk of cocaine toxicity and sudden death. Most deaths are due to convulsions, respiratory failure or cardiac arrhythmias.

Chronic poisoning produces anorexia, emaciation, tremors, hallucinations and insanity. Associated with these are disturbances of sensation and emotion.

Cocaine is a very effective but toxic surface anaesthetic and is used only occasionally in surgery of the nose, throat and eye in the concentrations of 5 to 10 per cent. Allergic reactions to this drug are frequent.

There are many new synthetic local anaesthetics. Since many of these have no clear advantage over the established ones, only the commonly used drugs are discussed below.

PROCAINE I.P. (Novocaine): It is the diethyl

aminoethyl ester of para aminobenzoic acid. It is non-irritant and as effective as cocaine. It is much less toxic and does not produce drug dependence.

Its disadvantages are that it is poorly absorbed from the mucus membranes and, therefore, has no topical use. It has a vasodilator property.

Procaine is rapidly hydrolysed by certain enzymes in the plasma and liver and is partly excreted in the urine, conjugated with glucuronic acid and glycine.

LIGNOCAINE I.P. (Xylocaine, Lidocaine): This is the most commonly employed drug. It is stable, can be stored for a long time at room temperature and can be autoclaved repeatedly. It has a quick onset of action, a high degree of penetration and its toxicity is similar to that of other local anaesthetics in equipotent doses. It is also an excellent surface analgesic. Following infiltration of 0.25-0.5% solution, the duration of action varies between 30 and 60 minutes. Addition of adrenaline (1 in 200,000) prolongs the action for about 2 hours. Analgesia is complete within a few minutes and recovery occurs quickly, within 2-3 hours after spinal anaesthesia. The drug is recommended for topical use, nerve blocks, infiltration and epidural injection and for dental analgesia. It may cause drowsiness but has no action on the blood vessels. It equals procaine in toxicity in a concentration of 0.5 per cent but is probably a little more toxic in higher concentrations. It can be used in subjects allergic to procaine and other ester-type local anaesthetics. Its use in cardiac arrhythmias is discussed in Chapter 25.

AMETHOCAINE I.P. (Tetracaine, Pontocaine) is a long acting and powerful local anaesthetic. Its long duration of action following spinal injection makes it less suitable than lignocaine for operation of shorter duration. It is effective when applied topically; its absorption from the vascular mucous membranes is very rapid and deaths have been reported following its use in urethra and respiratory tract. It should never be used on inflamed, injured or very vascular surfaces.

BUPIVACAINE (Marcain): This local anaesthetic is about four times as potent as lignocaine and has more prolonged action. Its toxicity is similar to that of lignocaine. It is used for spinal anaesthesia and epidural analgesia. It is available in the concentration of 0.25% and 0.5%.

MEPIVACAINE has N-methyl substituent in the place of the butyl group of bupivacaine.

CINCHOCAINE (Dibucaine, Nupercaine) is a potent but toxic local anaesthetic. It is not used for infiltration or nerve block anaesthesia. It can be used locally in the form of ointment and as light and heavy solutions for spinal anaesthesia.

The concentrations in which various local anaesthetics are used are given in Table 12.1. An *ideal local anaesthetic* should be safe and efficient for the purpose it is used for; it should have a quick onset of action with sufficiently long duration, it should be stable, easily sterilizable and inexpensive. Associated vasoconstriction is desirable. However, there is no such ideal local anaesthetic agent.

Section IV : Autonomic Nervous System

13 General Considerations

Autonomic nervous system was so named by Langley (1898), because of the fact that unlike the somatic nervous system of the skeletal muscles, it is independent of volitional control and thus enjoys some degree of autonomy.

The autonomic nervous system (ANS) innervates the heart, the smooth muscles, the glands and the viscera and governs the functions of these organs. Unlike the somatic structures, the structures receiving the autonomic nerve supply possess an inherent physiological activity and the nervous influences only augment or reduce the initial functional level. Interference with autonomic nerve supply, therefore, does not completely abolish the vegetative functions. This is in contrast to skeletal muscles which develop total paralysis and atrophy following interruption of their motor supply. The presence of this inherent physiological activity appears to be a built-in protective mechanism.

The autonomic nervous system comprises two broad divisions, the *parasympathetic* and the *sympathetic*. Usually, these two systems are in a state of dynamic equilibrium, the parasympathetic mainly participating in tissue building reactions while the sympathetic enables the individual to adjust to stress and prepares the body for 'flight or fight'. An animal can survive complete elimination of sympathetic but not of parasympathetic nervous system.

The control of autonomic functions is represented at all the levels of the central nervous system. The reason for this phenomenon appears to be phylogenetic. Thus, an animal or a man with

the absence of entire neuraxis except the spinal cord is still capable of maintaining blood pressure and other vegetative functions except respiration. The autonomic functions are regulated through the reticular formation and its constituents, along with the cranial nerve nuclei. In the hypothalamus, the posterior and the lateral nuclei are regarded as being associated with sympathetic activity while the parasympathetic function is modulated by the midline nuclei. The thalamus, the centre and relay station for sensory perception, can modify the autonomic activity through its numerous connections. The limbic system is postulated to coordinate the autonomic reactions with emotions but the ultimate synchronization of the somatic and vegetative functions is undoubtedly achieved in the cortex.

The autonomic innervation, irrespective of whether it belongs to the parasympathetic or the sympathetic nervous system, consists of a myelinated *preganglionic fibre* which forms a synapse with the cell body of a non-myelinated, second neurone, termed the *postganglionic fibre*. The postganglionic fibre in turn terminates in a synapse with the receptors of the organ supplied by it. The *synapse* may thus be defined as a structure that is formed by the close apposition of a neurone either with another neurone or with effector cell. The synapse is specialized for transmission of excitation or inhibition. The synapse between the preganglionic and postganglionic fibres is termed as a *ganglion* while that between the postganglionic fibre and the receptors is termed the *neuroeffector junction*. Unlike the somatic synapses,

the autonomic synapses are outside the cerebrospinal axis. It must be emphasised that the synapse is a physiological and not an anatomical continuity. Passage of an impulse across a synapse is carried out by the process of *transmission* while it is carried along the preganglionic or postganglionic fibres by the process of *conduction*.

DISTRIBUTION OF PARASYMPATHETIC NERVOUS SYSTEM

The parasympathetic nervous system serves two important functions:

(a) It carries the afferent impulses from the viscera which reflexly modify the autonomic functions, and

(b) It supplies motor fibres to smooth muscle, glands, heart and viscera through its craniosacral outflow.

(a) Visceral afferents: The visceral afferent fibres are non-myelinated. They mediate visceral sensations except pain, regulate vasomotor, respiratory and viscerosomatic reflexes and coordinate the autonomic activity in general. The important afferents are:

(i) Afferents from the carotid sinus and carotid body carried through the glossopharyngeal nerves. Stimulation of these afferent fibres occurs as a result of local elevation of blood pressure or decrease in blood pH; this results in a fall in blood pressure and bradycardia (carotid sinus reflex) and stimulation of respiration (carotid body reflex) respectively. Hypotension is attributed to a reduction of sympathetic outflow and bradycardia occurs through increased vagal tone. Respiration is stimulated by increased activity of the medullary respiratory centre.

(ii) Stimulation of the afferent fibres of the aortic arch, carried through the vagus nerve, also produces hypotension by reducing peripheral sympathetic outflow while the stimulation of chemo-receptors of the aortic body induces respiratory stimulation.

(iii) The vagus carries afferent fibres from the lungs, heart and the gastrointestinal tract. These

afferents mediate visceral sensations. The reflex responses vary from hypotension (Bezold Jarisch reflex) to vomiting (afferents from stomach).

(b) Craniosacral outflow : The craniosacral outflow, mainly efferent in nature, consists of

(i) Midbrain or tectal outflow through the Edinger Westphal nucleus of the oculomotor nerve which terminates in the ciliary ganglion of the orbit. The postganglionic fibres supply the ciliary muscle and the circular fibres of sphincter pupillae.

(ii) Medullary outflow comprising of parasympathetic components of the facial, glossopharyngeal and vagus nerves. The facial nerve supplies secretomotor and vasodilator fibres to the submaxillary and sublingual salivary glands and probably also to the lacrimal glands. The glossopharyngeal carries the parasympathetic supply of the parotid glands via the otic ganglion, while the vagus provides secretomotor and vasodilator fibres for the viscera of the thoracic and the abdominal cavity with the exception of the lower third of the gastrointestinal tract.

(iii) The sacral outflow consists of axons arising from the second, third and fourth sacral segments of the spinal cord and forms the pelvic nerve which synapses near or within the bladder near lower third of the gastrointestinal tract including the rectum and the sexual organs, and supplies secretomotor and vasodilator fibres to these organs.

The distribution of the parasympathetic nervous system is much more limited than the sympathetic nervous system. The terminal ganglia of the parasympathetic nervous system are usually located near, on or in the innervated tissue. Usually, a single preganglionic parasympathetic fibre synapses with a single postganglionic cell body of the same system. A notable exception to this rule is the vagus nerve, the preganglionic fibres of which synapse with approximately 8000 ganglion cells in the Auerbach's plexus of small intestine.

DISTRIBUTION OF SYMPATHETIC NERVOUS SYSTEM

The sympathetic division consists of the thoracolumbar outflow. The cells of the preganglionic sympathetic fibres are situated in the intermediolateral column of the spinal cord and extend from the 8th cervical to the 2nd or 3rd lumbar segments.

The sympathetic ganglia are of five types:

- (a) Paravertebral
- (b) Prevertebral
- (c) Terminal
- (d) Intermediate
- (e) The adrenal medulla

(a) **Paravertebral ganglia** consists of 22 pairs of ganglia that form a lateral chain on either side of the vertebral column. The preganglionic sympathetic fibres emerge from the vertebral column along with the anterior spinal roots and end in the paravertebral ganglia as *white rami communicantes*. The ganglia give rise to *gray rami communicantes* which carry secretomotor fibres along the anterior spinal roots to sweat glands, pilomotor muscles, blood vessels of skeletal muscles and of the skin.

The first three pairs of the vertebral ganglia are termed as superior, middle and inferior cervical ganglia which mainly innervate the radial muscle fibres of the sphincter pupillae, sublingual and submaxillary salivary glands and supply vasodilator and pilomotor fibres to the skin of face and neck. The sympathetic innervation of the lacrimal and parotid glands is doubtful. The fourth pair of the paravertebral ganglia is called the *stellate ganglia*.

(b) **The prevertebral ganglia** lie in the abdomen and the pelvis. They are the coeliac, superior and inferior mesenteric and aortico-renal ganglia. The postganglionic fibres from these supply the abdominal viscera, the urinary bladder and the external genitalia.

(c) **The terminal ganglia** are small in number and are distributed in close proximity to the viscera such as urinary bladder and the rectum.

(d) **The intermediate ganglia** are closely

associated with the anterior spinal roots and lie outside the paravertebral ganglia.

A preganglionic adrenergic fibre may end in any of these ganglia. Thus, many of the preganglionic fibres arising from the 5th to the 12th thoracic segment do not synapse in the paravertebral ganglia but form the splanchnic nerves which mostly synapse into the coeliac ganglion.

The postganglionic sympathetic fibres from the upper thoracic ganglia (1st to 4th thoracic) form cardiac, oesophageal and pulmonary plexuses and thus end as arborizations in these organs.

(e) **The adrenal medulla** is anatomically, embryologically and functionally a sympathetic ganglion. However, it does not have a postganglionic continuation and serves a secretory function.

IMPULSE TRANSMISSION

It has been well established that transmission of an impulse across the synapse in central and peripheral nervous systems occurs mainly as a result of release of a neurohumoral transmitter substance into the synaptic cleft. Electrical transmission of impulses has, however, been demonstrated in lower organisms like crayfish and annelids. Such an electrically transmitting synapse is termed *ephapse*. In the ciliary ganglion of the chick both electrical and humoral impulse transmission have been demonstrated.

Neurohumoral transmission:

Dubois Raymond in 1877 was probably the first investigator to suggest that junctional transmission could be either chemical or electrical, more probably the former, while Kuhne (1888) postulated that the motor end plate of the skeletal muscle was excited as a result of the action current of the nerve impulse. Elliott (1904), a student of Langley, suggested that sympathetic nerve impulses acted by liberating adrenaline at the nerve endings supplying smooth muscles. In 1905 Langley postulated the presence of excitatory and inhibitory 'receptor substances' in the effector cell and Dixon (1906) proposed that parasympathetic

nerve impulses acted by liberating muscarine-like substance.

The pioneer investigations of Otto Loewi (1921) and Loewi and Navratil (1926) showed that the vagus inhibited the heart by means of a chemical transmitter acetylcholine. Loewi allowed the perfusion fluid from a frog heart (donor) to come into contact with a second frog heart (recipient). Stimulation of the vagosympathetic trunk of the donor frog produced cardiac arrest of both the donor and the recipient heart. As no anatomical communication existed between the donor and the recipient hearts, Loewi proposed that the arrest of the recipient heart was brought about by a substance released into the perfusion fluid from the donor heart on vagosympathetic stimulation. This substance was initially termed *vagusstoff*. Loewi presented evidence which established it as acetylcholine. He also noted that if the vagosympathetic trunk of the donor heart was stimulated after its initial atropinization, both the donor and the recipient heart accelerated. This led him to postulate another substance, released from the atropinized donor heart following vagosympathetic stimulation. He named this substance as *acceleransstoff*. Support for the release of an accelerator substance on nerve stimulation came from the work of Cannon. The accelerator neurohumoral transmitter was established as noradrenaline by Von Euler (1946).

The work of Dale, Feldberg, Gaddum and others led to the extension of the chemical transmitter hypothesis to the autonomic ganglia and myoneural junctions where acetylcholine was identified as the transmitter.

Barger and Dale (1910), while describing the pharmacological actions of adrenaline and related substances, employed the term *sympathomimetic* as these actions resembled those seen following sympathetic stimulation: similarly the actions of pilocarpine, muscarine and related substances were described by them as *parasympathomimetic*. Dale in his later work (1914) used the term '*Nicotinic action*' to describe the ganglionic and neuromuscular actions of acetylcholine and '*Muscarinic action*' to describe the actions at the

postganglionic parasympathetic nerve endings, because of their resemblance to those observed following the alkaloids, nicotine and muscarine respectively.

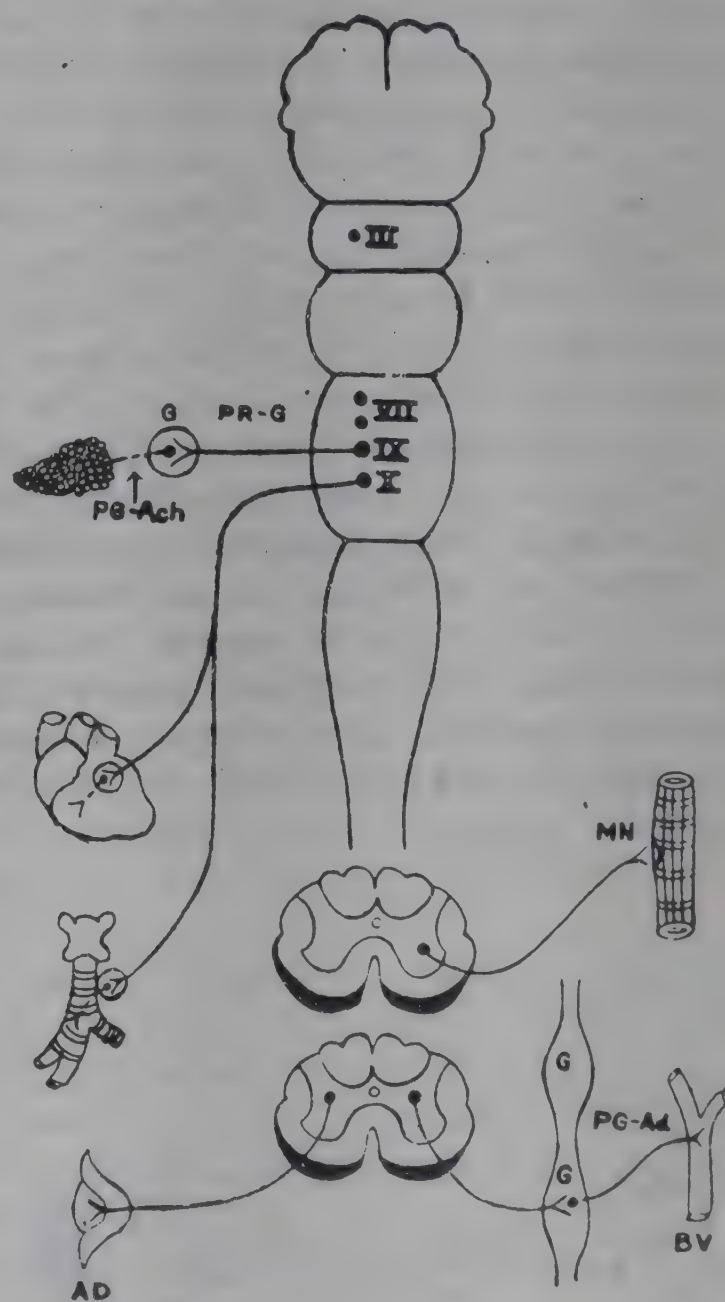


Fig. 13.1 Schematic representation of the sites of release of neurohumoral transmitters acetylcholine (ACh) and noradrenaline. ACh is released at all the ganglia (G), postganglionic cholinergic nerve endings (PG-Ach), myoneural junctions (MN) and the adrenal medulla (AD). Noradrenaline is released at postganglionic adrenergic nerve endings (PG-Ad), adrenaline is released from the adrenal medulla.

Since the terms sympathetic and parasympathetic do not give any idea about the chemical transmitter at the nerve endings, Dale classified autonomic nerves as either (a) *adrenergic*, which release noradrenaline and (b) *cholinergic*, which release acetylcholine.

A neuron can receive chemical messages at various active sites called receptors, two groups of which are considered important. The first group, located on the cell body and dendrites, is called *soma-dendritic receptors* which, when acted upon, primarily modify the functions of the soma-dendritic region such as generation of action potential or protein synthesis. The second group is located in or near the axon terminals and is called *presynaptic receptors*; these receptors, when activated, primarily modify the function of the terminal region, such as facilitation or inhibition of transmitter release and synthesis. Presynaptic receptors occur on neurons containing biogenic amines, amino acids and peptides; their activity can be modulated not only by blood borne agents but also by the neuron's own transmitter which is thus involved in '*synaptic feed back mechanisms*'. Such presynaptic autoreceptors have been postulated for noradrenaline, adrenaline, dopamine, 5-HT, acetylcholine and GABA neurons.

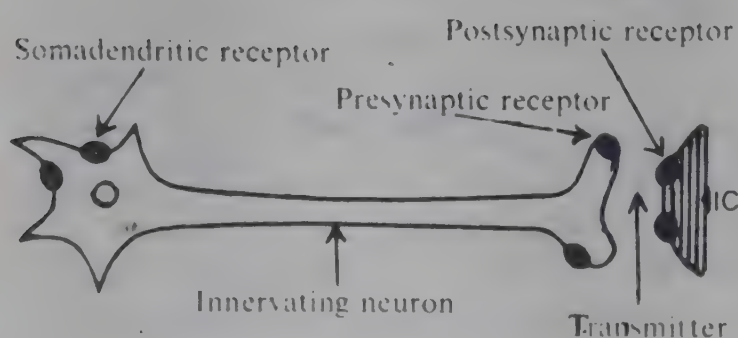


Fig 13.2 : Pre- and Postsynaptic receptors

NEUROHUMORAL TRANSMITTERS

The neurohumoral transmitters definitely es-

tablished at present are:

- (1) Acetylcholine
- (2) Noradrenaline and Dopamine

The criteria which a biologically active substance must satisfy to be termed as neurohumoral transmitter have been mentioned in Chapter 3.

Acetylcholine : Acetylcholine, an ester of choline, was recognised as an extremely potent pharmacological substance by Hunt in 1906. Acetylcholine acts as the neurohumoral transmitter at :

- (i) all the preganglionic fibres of ANS i.e. at both the sympathetic and parasympathetic ganglia,
- (ii) the postganglionic parasympathetic nerve endings,
- (iii) the sympathetic postganglionic nerve endings, supplying sweat glands in humans and cats,
- (iv) the somatic motor nerve endings, supplying skeletal muscles,
- (v) the nerve endings supplying adrenal medulla and
- (vi) between certain neurones within the brain and the spinal cord. The present evidence indicates that transmission from the motor neurone collateral to the Renshaw cells is cholinergic and the receptors are predominantly nicotinic. In contrast, most of the cholinergic neurones at higher levels of the CNS have predominantly muscarinic receptors.

According to the Burn and Rand hypothesis, stimulation of sympathetic fibres results first in the release of acetylcholine, which, in turn causes the release of noradrenaline to act on the effector organ. This concept, however, is not well established.

Acetylcholine is synthesized inside the nerve fibre by combination of choline with an acetyl group. The acetyl group is obtained from acetyl-coenzyme A, a product of the intermediary metabolism. The coupling of choline with the acetyl

group is catalyzed by the enzyme *choline acetylase*. The synthesis of acetylcholine by choline acetylase is thus mainly dependent upon the continued supply of choline and glucose, the latter being essential for synthesis of coenzyme A.

Acetylcholine is hydrolysed into choline and acetic acid by the enzymes termed choline esterases. Two main types of cholinesterases have been identified. (1) *acetylcholinesterase*, or *true cholinesterase*, present in neurones, ganglia and at myoneural junctions, which rapidly hydrolyzes acetylcholine and another choline ester, acetyl beta methacholine (methacholine) but not benzoylcholine and (2) *butyrylcholinesterase* or *pseudocholinesterase*, present mainly in the plasma, liver and other organs, which hydrolyzes acetylcholine slowly, but not methacholine. The activity of the cholinesterases can be inhibited by the anticholinesterase drugs which are discussed elsewhere.

Steps involved in the synthesis of the neuro-humor, its metabolism and its interaction with the receptors are potential points where a drug can act. The latter can thus mimic or antagonize the action of the corresponding neurohumor.

The presence of acetylcholine in biological fluids can be detected by:

(a) Contraction of the dorsal muscle of leech and rectus abdominis muscle of the frog.

(b) Loss of this activity by addition of plasma or tissue extracts (these contain cholinesterases) to the biological fluid.

(c) Retention of activity in an acidic medium and its loss in an alkaline medium.

(d) Enhancement of the activity by anti-cholinesterase and its blockade by blocking agents like atropine, ganglion blocking agents and d-tubocurarine.

Noradrenaline and Dopamine: Noradrenaline and dopamine act as neurohumoral transmitters at the post-ganglionic sympathetic nerve endings and certain regions within the brain. These amines are present in highest concentration in the terminal axonal processes of specific neurones, where they are synthesized and stored in the vesicles within the varicose axon terminals.

The three catecholamines, noradrenaline, adrenaline and dopamine are synthesized from the amino acid phenylalanine as follows:

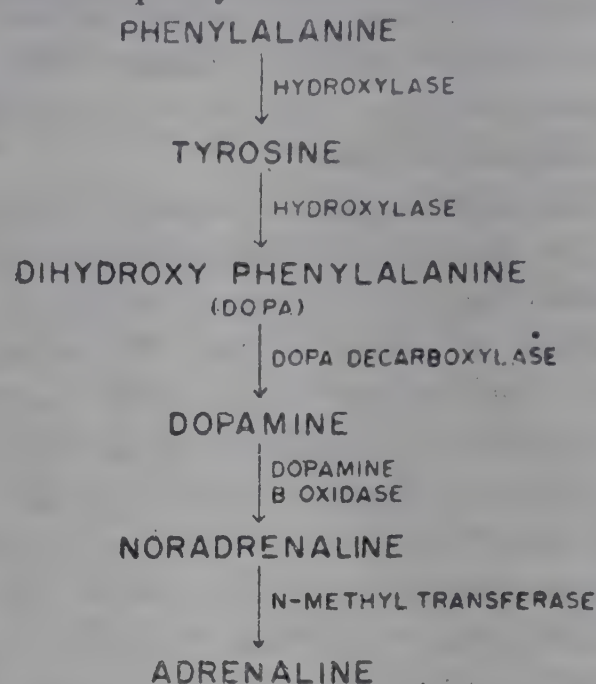


Fig 13.3: Biosynthesis of catecholamines.

Adrenaline is formed in the adrenal medulla by methylation of noradrenaline. The enzymes involved in their synthesis have been depicted in Figure 13.3. The conversion of tyrosine to DOPA, catalyzed by the enzyme *tyrosine hydroxylase*, is probably the rate limiting step which sets the pace for the biosynthesis of the neurotransmitters. Tyrosine hydroxylase disappears from the tissues if the sympathetic nerves degenerate. Alpha-methyl tyrosine and 3 iodotyrosine are inhibitors of this enzyme.

It should be pointed out that the enzymes involved in noradrenaline and adrenaline biosynthesis are not very specific. Thus, dopa decarboxylase catalyzes the conversion of 5-hydroxytryptophan to 5-hydroxytryptamine and of histidine to histamine.

Unlike acetylcholine, noradrenaline released into the synaptic cleft is only partially destroyed and a part is taken up again by the sympathetic nerve endings. The mechanism of noradrenaline metabolism is discussed elsewhere. The end-products of noradrenaline and adrenaline metabolism are excreted in urine in a free form and as conjugates of glucuronic and sulfuric acids.

The two main dopaminergic pathways are (i) nigrostriatal dopamine fibres originating from

the cell bodies in the substantia nigra and (ii) the meso-limbic dopamine system originating mainly from dopamine cell bodies surrounding the interpeduncular nucleus. Degeneration of the former causes Parkinson's disease while many psychoactive drugs are known to modify the functions of the latter.

Adrenaline, which was initially believed to be the sympathetic transmitter, has been shown to be released into the blood stream, mainly on stimulation of the adrenal medulla. The adrenal medulla is innervated by preganglionic sympathetic neurons whose cell bodies are located in the spinal cord segments T₃ to L₃. People who have spinal cord transection at the level of T₃ or above have reduced plasma levels of adrenaline. The hypothalamus plays an important role in the regulation of catecholamine secretion by adrenal medulla. Stimulation of the splanchnic nerves results in the release of ACh from the nerve endings which, by increasing the permeability of the chromaffin cells to calcium ions, increases the intracellular calcium and causes the secretion of catecholamines. Calcium is thus, important both for the release of ACh from nerve endings and for the secretion of catecholamines by chromaffin cells.

Because of their unique blood supply, the adrenal chromaffin cells are exposed to unusually high concentrations of glucocorticoids in the venous drainage from the adrenal cortex. Glucocorticoids cause the induction of the enzyme noradrenaline N-methyltransferase and thus control the rate of synthesis of adrenaline. Catecholamines stored in chromaffin granules constitutes about 6% of the dry weight of the adrenal medulla.

A variety of physical and emotional stimuli can give rise to adrenal catecholamine secretion. In addition, the secretion increases in response to various circulating substances such as glucagon, histamine, angiotensin II and bradykinin; this however, appears to occur only under some pathological situations.

Mechanisms of neurohumoral transmission: The development of electron micros-

copy, new histochemical techniques and intracellular recordings of electrical potentials has no doubt greatly helped to elucidate the ultrastructure and physiology of the neurone and the synapse but has made the problem of neurohumoral transmission infinitely more complex.

The space between the pre- and post-ganglionic fibres or that between the nerve ending and the receptor is termed the *synaptic cleft*. At the ganglion, the synaptic cleft is limited by the pre- and postsynaptic membranes while at the neuro-effector junction, it is circumscribed by the surface membrane of the nerve terminal on one side and the receptor region on the other.

The terminal portions of the pre- and post-ganglionic cholinergic axons have been shown to contain spherical or oval vesicles, known as the *synaptic vesicles* in addition to mitochondria. The synaptic vesicles tend to be aggregated close to the synaptic cleft.

It is proposed that acetylcholine is synthesized by the choline acetylase of the synaptic vesicles. This acetylcholine is termed *depot acetylcholine*, approximately 25 per cent of which is released into the synaptic cleft from the vesicles as a result of nerve impulse. This is "releasable" acetylcholine. Acetylcholine which is not releasable serves the function of replenishing the stores of releasable acetylcholine. It has been demonstrated that depending upon the intensity of the nerve impulse, the number of synaptic vesicles discharging their acetylcholine content increases. As acetylcholine is present in the vesicles in a highly concentrated form, it also inhibits further synthesis of acetylcholine by the vesicles; emptying of a vesicle stimulates the synthesizing activity.

It has been suggested that small quantities of acetylcholine are released continuously into the synaptic cleft and are responsible for the post-junctional miniature end plate potentials recorded intracellularly. Acetylcholine released into the synaptic cleft as a result of nerve impulse produces a change in permeability of the postsynaptic membrane or the receptor, leading to its depo-

larization by ionic fluxes. Thus, with inward flux of sodium and outward flux of potassium as a result of altered permeability with acetylcholine action, the negativity of the intra-axonal voltage diminishes and this produces a nerve action potential or a potential in the receptor that leads to either conduction of the nerve impulse across the axon or activation of the effector organ resulting into a secretory or a motor response.

Acetylcholine released into the synaptic cleft is rapidly destroyed by the true cholinesterase. This reverses the ionic changes and enables the postsynaptic membrane or the receptor site to get repolarized.

In myelinated fibres, the ionic fluxes occur only at the nodes of Ranvier and the nerve impulse is thus conducted in a leaping manner from node to node. This mode of conduction is termed *saltatory conduction*.

The maximum concentration of noradrenaline is found in the granulated vesicles in the varicosities of adrenergic nerve terminals in the brain as well as the peripheral adrenergic neurones. In place of the synaptic vesicles of the cholinergic nerve, the adrenergic neurone contains osmophilic granules also termed chromaffin granules because of their staining properties. These granules are believed to take up dopamine from the neuronal cytoplasm and convert it to noradrenaline. It seems that the noradrenaline in the adrenergic nerve terminals exists in several pools, the major portion, over 60 per cent being present in protein bound form as granules. In the granules it exists with calcium and ATP. After release, noradrenaline diffuses freely and passively from granules into the cytoplasm and then to the extracellular space. Its movement from the extracellular space back to the cytoplasm, however, involves active transport mechanisms. Calcium ions are believed to play an important role in the release mechanism. Thus, following a nerve impulse, noradrenaline is actively released from the granules into the synaptic cleft and to the receptors on the effector cells. Only a part of the stored noradrenaline is available for release into

the synaptic cleft as a result of nerve impulse. This portion is termed the 'mobile or functional pool' of noradrenaline and is in equilibrium with a 'fixed or non-functional pool' which replenishes it on depletion.

Little is known about the mechanisms involved in the regulation of the amount of neurotransmitter released upon arrival of nerve impulses. Recent studies indicate the existence of a presynaptic regulation of noradrenaline release through a negative feedback mechanism mediated by adrenergic alpha-receptors and a positive feedback mechanism mediated by presynaptic β -receptors. According to this hypothesis, beta-receptors are more sensitive to agonists so that during the initiation of release, low concentrations of noradrenaline in the synaptic cleft accelerate the release process. When the concentration of noradrenaline reaches adequately high levels, the presynaptic alpha-receptors, belonging to the so-called 'alpha 2' group, are stimulated and the secretion is terminated by a negative feedback mechanism. Alpha-receptor antagonists such as phenoxy-benzamine, on the other hand, enhance noradrenaline release. The combined effects of the positive and negative feedback mechanism may thus control the 'need oriented' release of the transmitter. Other such receptors of the alpha 2 type are located on the cell bodies of the adrenergic neurones and are responsible for inhibiting the activity of the neurones. It appears that a presynaptic regulating mechanism similar to that described in the periphery operates in the CNS as well. Further, similar mechanisms might exist for other neurotransmitters such as dopamine and acetylcholine. Drugs could produce actions by altering the release of these neurotransmitters centrally or peripherally, by modifying the presynaptic regulatory mechanisms. (See Chapter 3).

A small part of released noradrenaline is metabolized outside the cell by the enzyme catechol-O-methyl-transferase (COMT) but a large part (75-80%) is retaken into the cell by an active process and restored mostly in mobile pool. Only a little portion is metabolized intracellularly by

mono-amine oxidase (MAO). Rebinding of noradrenaline with the granules represents a way by which it is inactivated but used again. *In fact, physiologically, uptake and restorage are probably the major routes of noradrenaline inactivation and enzymatic destruction plays only a minor role.* The enzymes M.A.O. and C.O.M.T. are widely distributed throughout the body including the brain, with the highest concentrations in the liver and the kidneys.

There are reports postulating the existence of multiple forms of M.A.O. Noradrenaline and 5-HT are mainly oxidised by 'M.A.O.-A' form which can be selectively inhibited by very low concentration of inhibitor clorgyline. Benzylamine and β -phenylethylamine (PEA) are believed to be preferred substrates for 'M.A.O.-B' form; this form can be selectively inhibited by the drug l-deprenil. Tyramine and dopamine are substrates for both forms of the enzyme. The human liver contains both enzyme forms in equal amounts while the human brain M.A.O., like that of platelet, is believed to be predominantly type B.

Catecholamine uptake mechanisms and drugs: Many studies have now defined the properties of the catecholamine 'uptake' mechanisms involved and their modification by drugs. The uptake processes have been designated 'Uptake₁' and 'Uptake₂'. 'Uptake₁' is the picking up of catecholamines from the extracellular space by the axoplasm of the adrenergic neurons. This process demonstrates a greater affinity for noradrenaline than for adrenaline. Catecholamines taken up by 'Uptake₁' are then transferred to the storage vesicles in the adrenergic neurons by a separate process. 'Uptake₂' is the picking up of catecholamines by the effector cells in the peripheral tissues such as the vascular smooth muscle, the heart and the exocrine glands. Such uptake is followed by rapid degradation of the catecholamines. In contrast to 'Uptake₁', 'Uptake₂' demonstrates a higher affinity for adrenaline and isoprenaline than for noradrenaline. In the peripheral tissues, the extraneuronal sites for 'Uptake₂' are far more numerous than the neuronal uptake sites

for Uptake₁. 'Uptake₁' may be looked upon as 'uptake with retention'; by contrast, 'Uptake₂' is an 'uptake followed by metabolism' process whereby catecholamines are rapidly metabolized. 'Uptake₂' can be inhibited by various drugs such as normetanephrine, phenoxybenzamine and various steroids like corticosterone, estradiol, testosterone and cholesterol. Inhibition of monoamine oxidase (MAO) and/or COMT can also block 'Uptake₂' system. Experimentally, the actions of catecholamines on vascular smooth muscle, nictitating membrane and heart muscle are potentiated by steroids; thus, the actions of isoprenaline and noradrenaline on heart and aortic smooth muscle respectively are potentiated by hydrocortisone.

Many sympathomimetic amines are also taken up by 'Uptake₁' process and hence, can act as competitive substrates, thus inhibiting the noradrenaline uptake. Other important drugs which are known to inhibit the 'Uptake₁' mechanism of noradrenaline are tricyclic antidepressants (imipramine, amitriptyline), alpha receptor blocker (phenoxybenzamine), MAO inhibitors (tranylcypromine, phenelzine), adrenergic neurone blockers (guanethidine), chlorpromazine and cocaine. Some of these drugs produce their major therapeutic actions due to this blocking effect on 'Uptake₁'. Drugs that inhibit 'Uptake₁' potentiate and prolong the responses of sympathetically innervated organs to nerve stimulation. Indirectly acting sympathomimetic amines like amphetamine not only release noradrenaline from adrenergic nerve terminals but they also potentiate the actions of the released catecholamine by blocking its reuptake (See Fig. 13.4). Certain drugs like guanethidine which act as substrate for 'Uptake₁' when given in small doses, are selectively concentrated by adrenergic nerve terminals and cause a transmission block, thus reducing the effectiveness of sympathetic nerve discharge. Similarly, the drug 6-hydroxydopamine gets selectively accumulated through 'Uptake₁' process and produces selective destruction of adrenergic neurones (*chemical sympathectomy*) in both pe-

ripheral and central nervous system.

Thus, two distinctly separate but related systems exist at the level of adrenergic neurone. One is concerned with the *intraneuronal amine concentrating-storage mechanism* associated with amine granules and the other a *neurone membrane amine pump* responsible for the reuptake (Uptake_1 process) of noradrenaline, following its prior release from the nerve terminals or following the injection. The adrenergic neurone membrane amine pump is relatively non-specific and sodium-dependent. Various drugs known to act on the adrenergic neurone probably produce their effects by modifying the synthesis, storage and ' Uptake_1 ' mechanisms of noradrenaline as summarized below (Fig.13.4):

(1) By supplying an amine precursor e.g. Levodopa used in Parkinson's disease is a precursor of dopamine.

(2) By blocking the ' Uptake_1 ' of noradrenaline by inhibiting the pump e.g. Tricyclic antidepressants like imipramine used in the treatment of mental depression; cocaine.

(3) By promoting the release of noradrenaline from the storage sites e.g. Tyramine; Amphetamine.

(4) By modifying the storage of noradrenaline, leading to its depletion from the sites e.g. Antihypertensive drug Reserpine and a related compound Tetrabenazine.

(5) By blocking the release of noradrenaline from the binding stores in the terminals e.g. Guanethidine, a drug used in the treatment of hypertension.

(6) By promoting a synthesis of a false transmitter e.g. Alpha methyl-dopa.

(7) By blocking postsynaptic receptors e.g. adrenergic receptor blocking drugs.

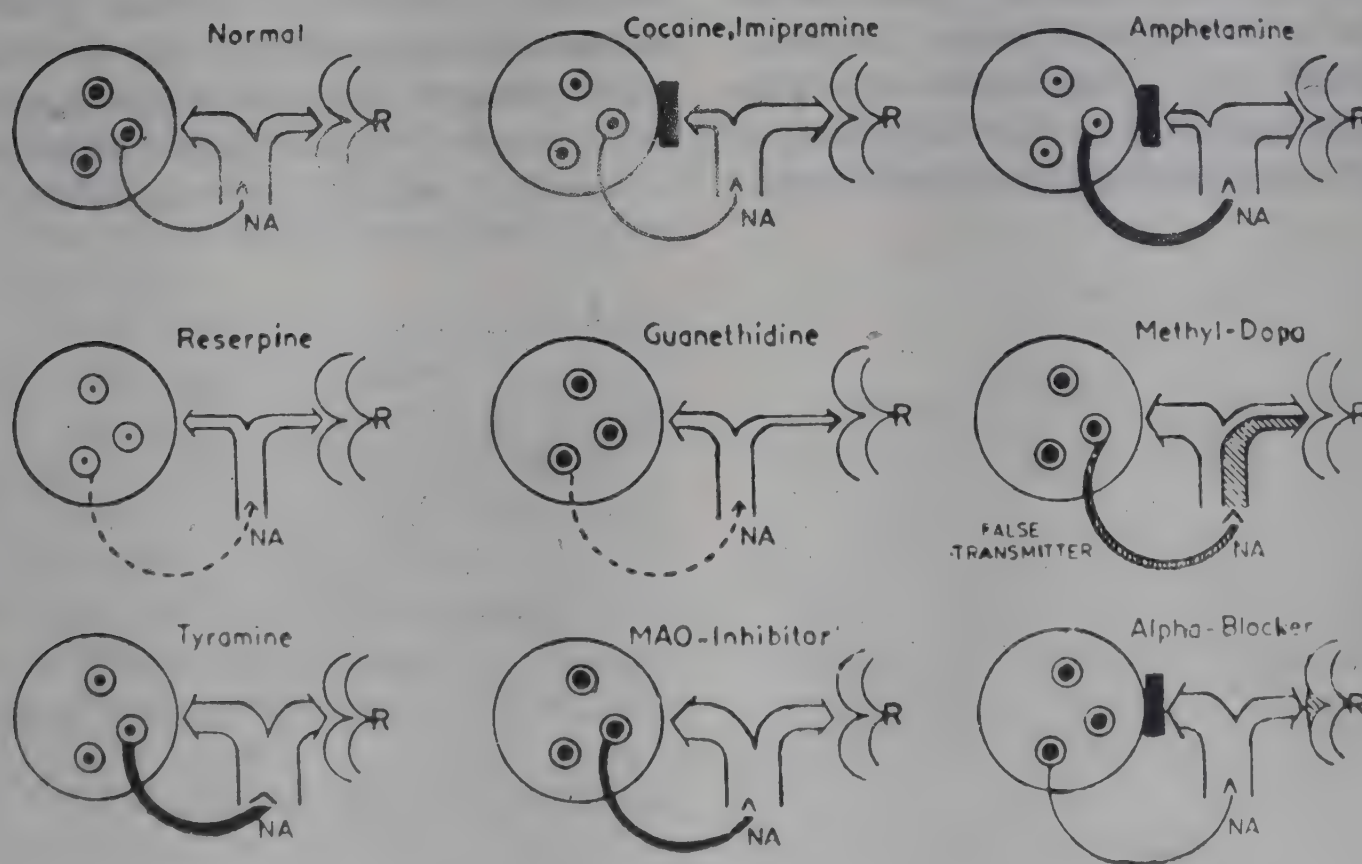


Fig. 13.4 Schematic diagram showing the effect of some drugs on noradrenaline (NA) uptake and release mechanisms. Drugs may act by promoting the NA release (amphetamine, tyramine), by inhibiting its Uptake_1 process (imipramine, cocaine, amphetamine), by depletion of NA from storage site (reserpine), by blocking the release from the storage site (guanethidine), by producing a false transmitter (methyl-dopa), by inhibiting the destruction of NA by monoamine oxidase and by blocking both Uptake_1 and Uptake_2 mechanisms (phenoxybenzamine).

(8) By *inhibiting the intraneuronal breakdown of noradrenaline* e.g. Monoamineoxidase (MAO) inhibitor drugs, used as antidepressants.

These mechanisms are discussed in detail elsewhere.

Specialized uptake mechanisms, similar to that described for noradrenergic neurones are also known to exist in dopaminergic and tryptaminergic neurones in CNS and in cholinergic neurones in the periphery and CNS. In cholinergic neurones, however, the transport mechanism is for transmitter precursor choline rather than for acetylcholine. The functional importance of dopamine and 5-HT uptake is not clear. It is possible that certain drugs like benztropine and related anticholinergic drugs owe some of their actions to an inhibition of dopamine uptake. Inhibitory action of tricyclic antidepressant drugs on 5-HT uptake at brain sites is discussed in Chapter 11.

Both acetylcholine and noradrenaline are also termed as *local hormones* because they act at the site of their synthesis. Other substances probably involved in neurohumoral transmission are histamine, 5-hydroxytryptamine, gamma aminobutyric acid and certain omega amino acids. The latter two are postulated to act as inhibitory and excitatory neurohumoral transmitters respec-

tively within the central nervous system.

Supersensitivity: Interruption of the nerve supply of an effector organ (denervation) makes it more sensitive to the neurohumor of the system supplying it. Thus, a skeletal muscle, after cutting the motor nerve, becomes highly sensitive to acetylcholine and the nictitating membrane becomes highly sensitive to noradrenaline after cutting its postganglionic sympathetic supply. This phenomenon is termed *denervation supersensitivity*. The exact mechanism is not known but it coincides with the failure of uptake of noradrenaline from the extracellular fluid. It may thus be related to the elimination of the neuronal uptake mechanism. It could also partly be due to degeneration of the nerve terminals after sectioning, leading to disappearance of enzymes that normally inactivate the transmitter and are closely associated with the nerve terminals. It may also be due to rise in receptor number induced by the fall in the catecholamine concentration within the synaptic cleft. Supersensitivity to transmitter substances occurs also after prolonged administration of blocking agents. Increased sensitivity resulting from interruption of preganglionic autonomic supply is termed *decentralization supersensitivity* and is of lesser magnitude.

14 Adrenergic and Adrenergic Blocking Drugs

The *sympathomimetic* or *adrenergic* drugs are agents that mimic the responses obtained as a result of stimulation of the sympathetic or adrenergic nerves. Majority of these substances contain an intact or a partially substituted amino (NH_2) group and hence, are also called as *sympathomimetic amines*.

From the therapeutic point of view these drugs can be classified as :

- (1) Adrenergic drugs used for raising blood pressure e.g. noradrenaline, metaraminol.
- (2) Those used as central stimulants e.g. amphetamine.
- (3) Those used as smooth muscle relaxants e.g. (a) adrenaline, isopropylarterenol, isoxsuprine and (b) selective beta-2 stimulants e.g. salbutamol.
- (4) Those used in allergic reactions e.g. adrenaline, ephedrine.
- (5) Those used for local vasoconstrictor effect e.g. adrenaline, naphazoline, phenylephrine.
- (6) Those used for suppressing the appetite (anorectic) e.g. fenfluramine, phenteramine.

These drugs can also be divided according to their structure into two broad groups :

(a) compounds with OH substitution in the 3 and 4 positions of the benzene ring (dihydroxybenzene compounds), termed as *catecholamines* (Fig.14.1) and

(b) those which lack the hydroxyl groups, known as *non-catecholamines*.

CATECHOLAMINES

The catecholamines include the sympathetic, neurohumoral transmitter noradrenaline, the

main hormone of the adrenal medulla adrenaline, dopamine, isopropylarterenol (isoprenaline) and N-methyl adrenaline. Catecholamine content of adrenal medulla normally is 85% adrenaline and 15% noradrenaline. In most cases of pheochromocytoma, a tumour of the adrenal medulla, the proportion of adrenaline in the medulla may markedly increase; extra-adrenal tumours, however, may predominantly secrete noradrenaline. Dopamine not only serves as a precursor of noradrenaline but also acts as a neurohumoral sympathetic transmitter in certain areas of the central nervous system. N-methyladrenaline has been detected in small quantities in adrenal glands of various animals but its physiological role appears uncertain. Isopropylarterenol (isoproterenol, isoprenaline) is a purely synthetic compound.

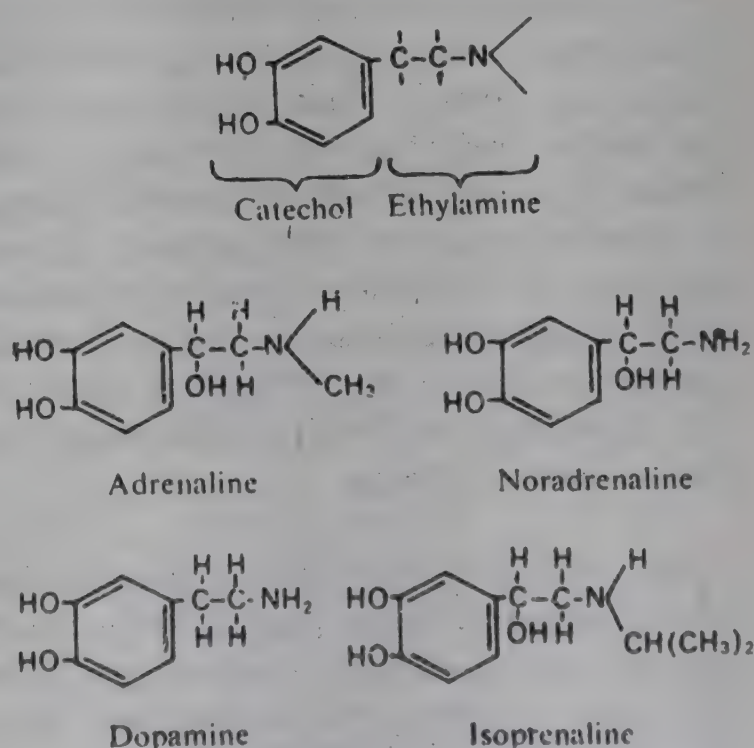


Fig. 14.1 :

The word 'nor' in noradrenaline was originally coined to indicate nitrogen (N) without (O-Ohne) a radical (R) in this case a methyl (CH₃) group.

Mechanism of action of catecholamines : The catecholamines produce their action by direct combination with receptors located probably on the cell membrane. The outcome of this drug receptor combination can lead to either an increase (excitation) or a decrease (inhibition) in the tissue activity. In order to explain these differences in responses by different tissues, the concept of two different receptors, *alpha* and *beta*, for catecholamine action was proposed by Ahlquist in 1948. Thus, the alpha receptor stimulation is believed to be mainly responsible for the excitatory effects of the catecholamines and they can be completely blocked by ergotoxine; the beta receptor stimulation usually produces inhibitory effects and these are not blocked by ergotoxine. Noradrenaline produces its pharmacological actions mainly by acting on the alpha receptors while adrenaline acts on both alpha and beta receptors; isopropylarterenol acts on beta receptors mainly. A given tissue may contain either alpha or beta or both types of receptors.

Even though it has been broadly stated that alpha receptors are excitatory and beta receptors inhibitory in character there are certain exceptions to this rule. Thus, beta receptors are predominantly present in the heart and are excitatory in character; their stimulation increases the rate and force of contraction of the myocardium. Similarly, both the alpha and beta receptors of the gastrointestinal tract are inhibitory in character; their stimulation produces a relaxation of the smooth muscle of the gut.

The concept of two separate receptors has been supported by newer synthetic drugs which can selectively block the effects resulting from stimulation of alpha or beta receptors. Thus, adrenergic receptors are classified according to their selective sensitivity to agonists and antago-

nists. Adrenergic receptors are located on the cell surface. As a general rule, beta-adrenergic responses appear to result from stimulation of a plasma membrane enzyme, adenylyl cyclase. This results in a rise of the intracellular cyclic AMP levels. The cyclic AMP acts inside the cell to alter the cellular function. The exact relationship between adenylyl cyclase and the hormone receptor is not clear. As compared to beta receptor, the nature of alpha-adrenergic receptor is much less understood. Most of the available evidence suggests that the alpha-adrenergic receptors utilize calcium ions as the 'second messenger' and that changes in cyclic AMP and cyclic GMP are secondary to the initial change in the calcium ions. Phosphodiesterase, another enzyme, promotes the breakdown of cyclic AMP. Drugs like caffeine, theophylline and other methyl xanthines which inhibit this enzyme are known to potentiate the beta receptor stimulant action of adrenaline.

On the basis of the relative selectivity and potency of both agonists and antagonists, two distinct beta receptors subpatterns could be distinguished; *beta*₁ receptors responsible for myocardial stimulation and lipolysis and *beta*₂ receptors responsible for bronchial muscle relaxation, vasodilatation and uterine inhibition. Similarly, alpha₁ and alpha₂ receptor subtypes have also been postulated. Alpha₁ receptors are predominant in vascular smooth muscle while alpha₂ receptors are believed to be responsible for inhibition of renin release from the kidney and for central alpha adrenergically mediated blood pressure depression. Presence of alpha receptors has been also demonstrated in non-neuronal tissues such as human leukocytes and platelets. The predominant receptors in various organs and the usual responses to their stimulation are given in the Table 14.1. These responses in isolated tissues may differ from those in the whole animal owing to the presence of reflex activity in the latter. Further, the initial condition of the tissue may also determine the resultant responses.

Pharmacological actions of adrenaline

and noradrenaline :

I. Cardiovascular system:

(a) *Heart*: Adrenaline, because of its stimulant effect on the predominant beta receptors of the heart, increases the rate, the force of contraction and the cardiac output. This is associated with increased metabolism of the myocardium with increased oxygen consumption, thus decreasing the cardiac efficiency. It abbreviates the cardiac systole. Extremely high cardiac rate, however, would prevent proper diastolic filling and may

produce fall in the cardiac output. Adrenaline abolishes the reflex vagal bradycardia in response to carotid sinus compression. It enhances conduction across the A-V node and may produce ventricular arrhythmias. Noradrenaline, however, usually does not increase the heart rate in an intact animal but tends to produce reflex bradycardia. It should be noted, however, that noradrenaline (see below) is the physiological transmitter in the heart and its capacity to stimulate cardiac β_1 receptors is

Table 14.1 : Distribution and responses of adrenergic receptors

Tissue		Response
I.	Predominantly alpha receptors	
	(a) Blood vessels:	
	Skin and mucosa	Constriction
	Cerebral	Constriction (slight)
	(b) Skin:	
	Pilomotor muscle	Contraction
	Sweat gland	Slight secretion
	(c) Radial muscle of iris	Contraction (mydriasis)
	(d) Salivary glands, except parotids	Thick, viscous secretion
	(e) Sex organ, male	Ejaculation
II.	Predominantly beta receptors	
	(a) Heart :	Increased heart rate (positive chronotropic action)
	S-A node - β_1	Increased contraction (positive inotropic action)
	Atria - β_1	Faster conduction
	A - V node - β_1	Increased contractility and conductivity, increased automaticity (positive dromotropic action)
	Ventricles - β_1	
	(b) Bronchial muscle - β_2	Relaxation
	(c) Skeletal muscle changes	Changes in contractility
III.	Both alpha and beta receptors	
	(a) G.I. tract :	
	Motility and tone (α_2 β_2)	Decreased
	Sphincters (alpha)	Contraction
	(b) Urinary bladder :	
	Trigone - alpha	Contraction
	Detrusor - β	Relaxation
	(c) Blood vessels :	
	Coronary - Alpha, β_2	Constriction; dilatation
	Pulmonary - Alpha, β_2	Constriction; dilatation
	Abdominal viscera - Alpha, β_2	Constriction (mainly); dilatation
	Renal - Alpha, β_2	Constriction; dilatation
	Skeletal muscle- Alpha, β_2	Constriction; dilatation
	(d) Adipocyte - α_2	Lipolysis
	Liver-Alpha, β_1 β_2	Glycogenolysis, neoglucogenesis
	(e) Leukocyte (human) - β_2	Inhibits chemotaxis and lysosomal enzyme release
	Platelet (human) - Alpha $_2$	Platelet aggregation

of vital importance.

The myocardial effects of adrenaline and noradrenaline can be blocked by the beta receptor blocking agents like propranolol.

(b) *Blood vessels and blood pressure:* The blood vessels of skin and mucous membranes are constricted by adrenaline and noradrenaline. Constriction of the blood vessels of the mucous membranes is usually followed by after-congestion. Adrenaline dilates the blood vessels of the skeletal muscles on account of the preponderance of β_2 receptors. The net result of these actions is a decrease in the total peripheral resistance. Thus, although adrenaline raises the systolic blood pressure by its cardiac actions, it lowers the diastolic pressure by its peripheral actions and hence, is not suitable in hypotensive shock.

As the rise in systolic blood pressure with adrenaline is only of moderate magnitude, compensatory reflexes do not antagonize the cardiac actions of adrenaline and the moderate rise in systolic blood pressure is accompanied by tachycardia, increased cardiac output and increased stroke volume.

The rise in systolic blood pressure produced by moderate doses of adrenaline is often followed by a fall. Adrenaline in such doses activates both

the alpha and beta receptors, the former being dominant in number. By stimulating the alpha receptors it produces a rise in blood pressure. However, the action of adrenaline on beta receptors is more persistent and hence, when the action on alpha receptors wears off, the action on beta receptors is unmasked producing a fall of blood pressure. This blood pressure response to moderate doses of adrenaline is termed '*biphasic response*'. Sir Henry Dale, working with ergot extracts, noted that this biphasic response was converted to the depressor response by prior administration of ergot extract. This was due to alpha receptor blocking action of ergot alkaloids, leading to stimulation of beta receptor by adrenaline and thus causing a fall in blood pressure. This phenomenon is termed as '*Dale's vasomotor reversal*'. (Fig. 14.3) Such reversal is not seen with noradrenaline.

Noradrenaline in an intact animal produces a rise in both systolic and diastolic blood pressure; the pulse pressure usually remains unaltered and the mean blood pressure increases. As compared to adrenaline, its β_2 receptor actions are very feeble. Noradrenaline induced hypertension is associated with bradycardia due to stimulation of the carotid baroreceptors.

Adrenaline and noradrenaline produce a sig-

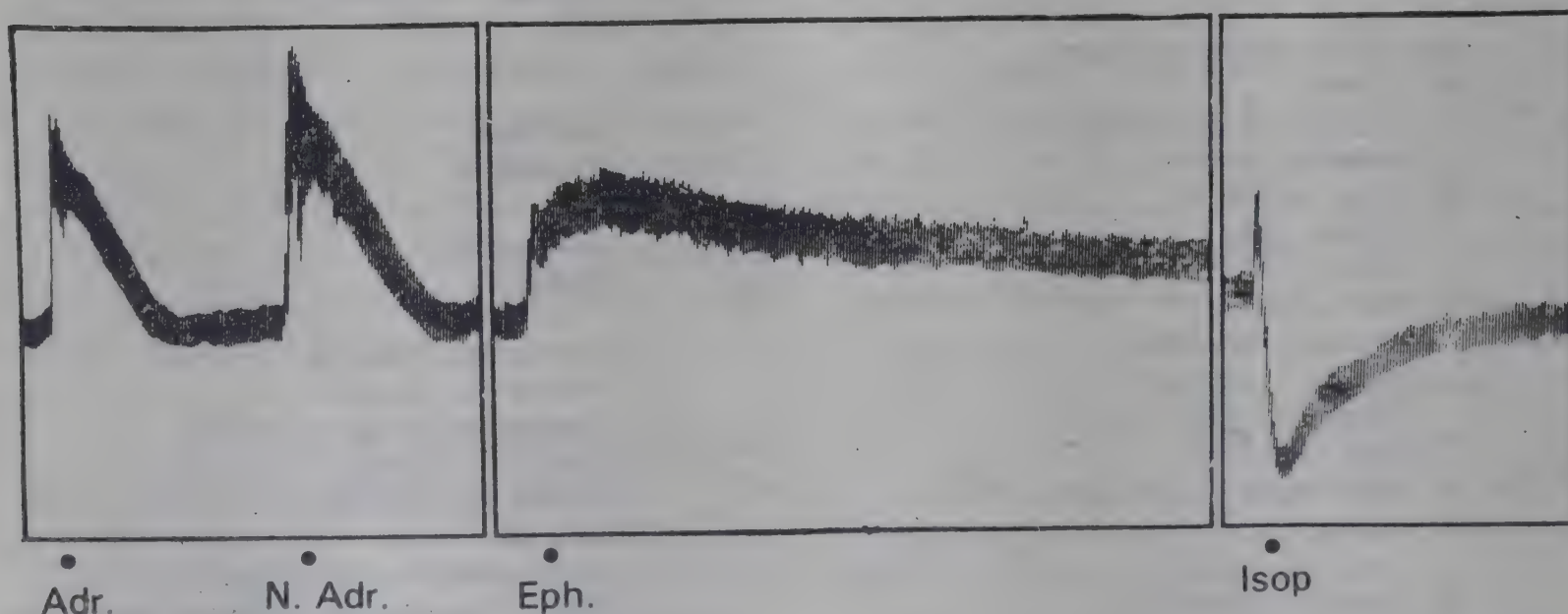


Fig. 14.2 : Effect of Adrenaline, Noradrenaline, Ephedrine and Isopropylarterenol on blood pressure in anaesthetised dog.

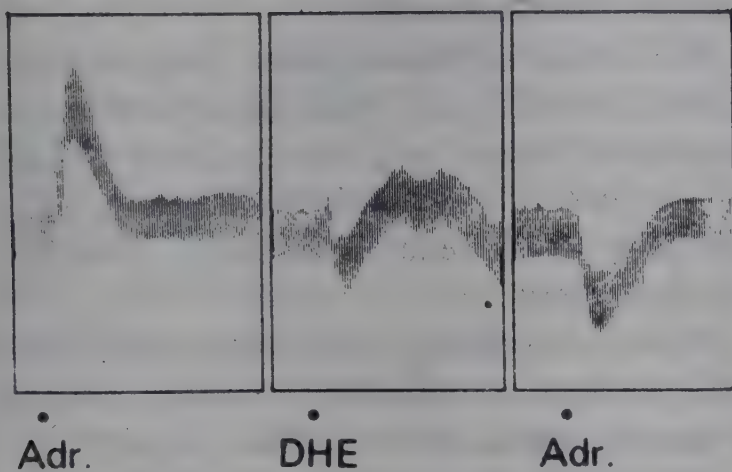


Fig. 14.3 : Dale's Vasomotor Reversal. Note the fall in B.P. with Adrenaline after injection of Dihydroergotamine (DHE).

nificant reduction in the renal blood flow in man even in doses that have no significant effect on blood pressure. The urine output is variably affected and urinary excretion of sodium, potassium and chloride is decreased. Renin secretion is increased.

Both adrenaline and noradrenaline constrict the hepatic and mesenteric blood vessels and raise the portal venous pressure. The pulmonary arterial and venous pressures are raised by both, more by adrenaline. This effect is partly due to pulmonary vasoconstriction and partly as a result of an increase in the left atrial pressure. Constriction of the musculature of the great systemic veins tends to push the blood from the periphery into the pulmonary circulation and this may occasionally result in pulmonary edema following adrenaline administration.

Adrenaline in moderate doses increases the cerebral blood flow and oxygen consumption, probably by increasing the systemic blood pressure. It probably increases the coronary blood flow by a complex mechanism; however, it cannot be used in coronary insufficiency because of its dominant cardiac actions.

II. Smooth muscle:

Bronchi: Adrenaline is a powerful relaxant of the bronchial smooth muscle. The spasm of bronchial muscle produced as a result of vagal stimulation, choline-esters, histamine or an antigen-antibody reaction, bradykinin, S.R.S., or

prostaglandin $F_2 \alpha$ is satisfactorily antagonized by adrenaline.

Uterus : The response of the uterus to the catecholamines varies according to species, the phase of oestrous cycle, presence or absence of gestation, period of gestation and the dose administered. The rat uterus is relaxed by these compounds irrespective of all these factors. The human non-pregnant uterus is stimulated to contract by adrenaline. In the last month of pregnancy adrenaline relaxes the human uterus.

Gastrointestinal tract : Adrenaline and noradrenaline relax the smooth muscles of the gut and reduce its motility. The relaxant effect of adrenaline is variable and too transient to have any therapeutic application.

Miscellaneous: Adrenaline contracts the pilomotor muscle of the hair follicle. It also produces a contraction of the vesical sphincter and the trigone, while relaxing the detrusor muscle. Adrenaline and noradrenaline produce contraction of the splenic capsule producing a release of erythrocytes into the peripheral circulation. This probably serves as a protective mechanism during stress such as hypoxia and haemorrhage.

III. Eye : Sympathetic stimulation results in mydriasis due to contraction of the radial muscle fibres of the iris and exophthalmos due to contraction of the orbital muscles. Nictitating membrane, present in lower mammals, contracts with adrenaline. Adrenaline, on topical application, does not readily produce mydriasis. It produces a moderate reduction in intraocular tension in the normal and the glaucomatous eye. Adrenaline has a more prominent effect on the eye than noradrenaline, but after denervation the response to noradrenaline exceeds that to adrenaline.

IV. Respiration : Besides being a bronchodilator, adrenaline is a weak stimulant of respiration. Given intravenously in man, both adrenaline and noradrenaline can induce apnoea partly by stimulating the baroreceptors and partly by a direct central action. Adrenaline, particularly in aerosol form, constricts the pulmonary vessel and relieves bronchial congestion; this results in

an increase in the vital capacity.

V. Metabolic effects : Adrenaline increases the blood sugar level by enhancing hepatic glycogenolysis and by decreasing the uptake of glucose by peripheral tissues. It also increases blood lactate by enhancing the breakdown of glycogen to lactate in the skeletal muscles. The free fatty acid concentration of plasma is raised by adrenaline as a result of increased breakdown of triglycerides in adipose tissues. Adrenaline produces a transient hyperkalemia followed by a more sustained hypokalemia. Of these metabolic effects mediated by β receptors, insulin release as well as liver and muscle glycogenolysis are probably mediated by β_2 receptors. Adrenaline inhibits insulin release by its α receptor stimulant action whereas it stimulates glycogenolysis by its

β receptor stimulant action.

VI. Central nervous system : The catecholamines do not cross the blood brain barrier satisfactorily and hence, their central actions are limited. Intravenous or intracarotid injection of adrenaline may produce excitement, stupor, vomiting and restlessness.

Neurones liberating noradrenaline and dopamine have been demonstrated in various areas of the central nervous system. (See Chapter 3)

VII. Skeletal muscle : Catecholamines influence skeletal muscle contractions by acting on both sides of the neuromuscular junction. The α -effect on the motor nerve ending increases the amount of ACh released and is probably the main factor in the improvement of neuromuscular transmission by adrenaline. The β -action on the

Table 14.2 : Comparison of the pharmacological actions of catecholamines in man

Effector organ	Adrenaline	Noradrenaline	Isopropyl arterenol
<i>Heart</i>			
Rate	++	-	++
Stroke volume	+++	++	+++
Cardiac output	+++	0, -	+++
Arrhythmias	+++	++	+++
Coronary blood flow	++	+	++
<i>Blood Pressure</i>			
Systolic	+++	+++	+, 0, -
Diastolic	+, 0, -	++	+, 0, -
Pulse	+, 0	++	0, +
Mean	+, 0	++	0
<i>Peripheral Blood Flow</i>			
Muscle	++	+, 0	++
Skin and mucous membrane	-	+, 0, -	+
Renal	-	-	?
Splanchnic	++	0, +	+, +
Cerebral	+	0, -	+
Total peripheral resistance	-	+++	-
<i>Smooth Muscles</i>			
Bronchi	+++	+, 0	+++
<i>Metabolism</i>			
Oxygen consumption	++	0, +	0
Blood sugar	+++	0, +	0
<i>Eosinopenic response</i>			
	+	0	0

+ = Increase, 0 = No change, - = Decrease.

muscle fibre itself probably contributes to the improvement of muscle contractions and tremor, sometimes observed following administration of these drugs.

VIII. Miscellaneous : Adrenaline produces a thick viscid secretion from salivary glands. It also produces leucocytosis and eosinopenia and accelerates blood coagulation. Adrenaline also stimulates platelet aggregation through alpha receptors in the platelets. Adrenaline and similar compounds inhibit the cellular anaphylactic mechanisms and thus tend to prevent the release of mediators of allergic bronchospasm such as histamine from the tissue mast cells.

The important pharmacological actions of the three catecholamines in man are summarized in Table 14.2.

Absorption, fate and excretion : Catecholamines are not administered orally because of their rapid inactivation in the gut and the liver.

On inhalation of adrenaline or isopropylarterenol aerosols, small quantities may be absorbed into the systemic circulation.

Adrenaline is mainly metabolized by two enzymes, catechol-O-methyl transferase (COMT), located extracellularly and monoamine oxidase (MAO), situated inside the mitochondria of the adrenergic neurones. COMT changes adrenaline into metanephrine and noradrenaline to normetanephrine. MAO oxidises these products into 3-methoxy-4-hydroxymandelic acid (vanilylmandelic acid or VMA) which is excreted in urine. A small quantity of catecholamines is excreted unchanged.

The normal 24 hour urinary excretion of VMA and free catecholamines is 4-8 mg. and 50-100 µg. respectively. A significant increase in these values is considered diagnostic of pheochromocytoma, an adrenal medullary tumor, producing excessive catecholamines.

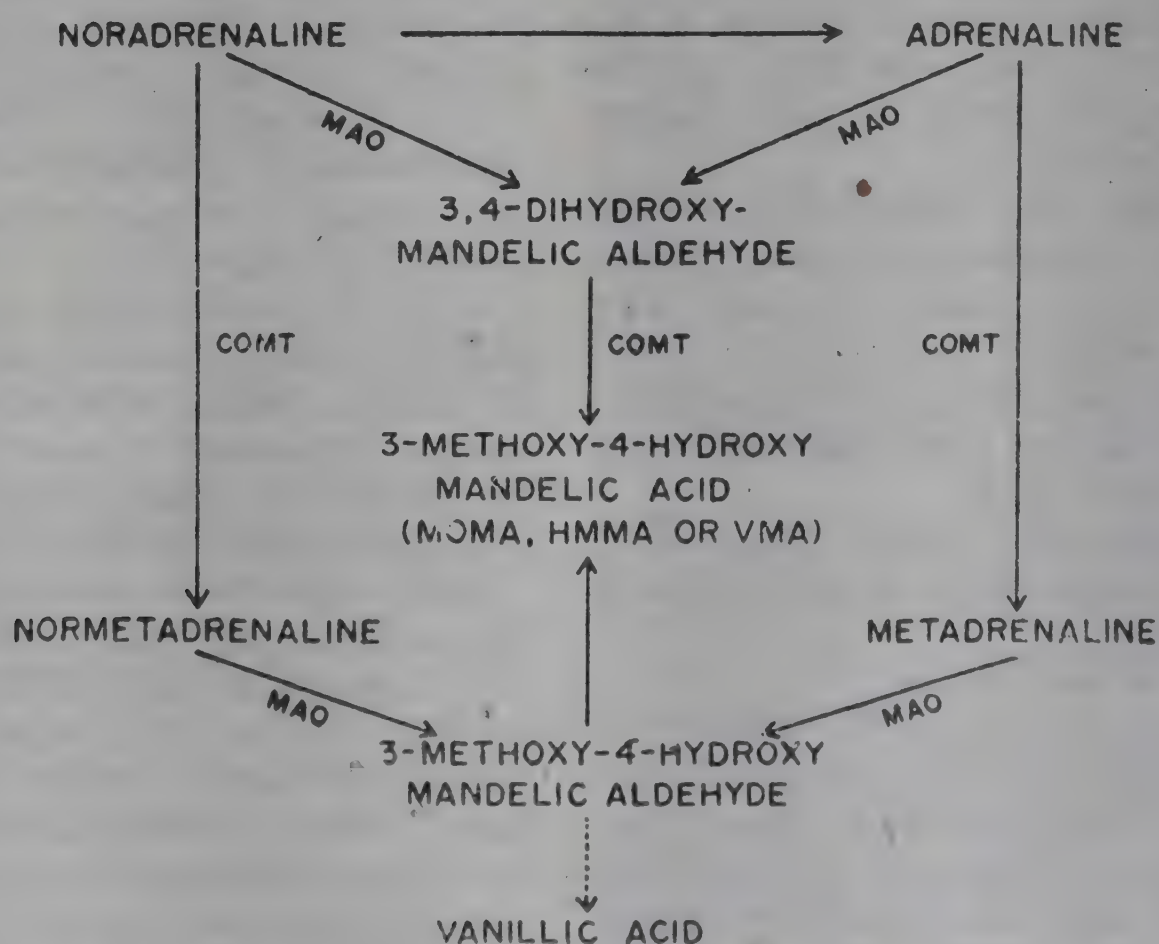


Fig. 14.4 : Metabolism of Adrenaline and Noradrenaline

Adverse reactions : Adrenaline, given subcutaneously, may occasionally produce palpitation and tremors. Noradrenaline, employed in the form of intravenous drip, may cause anxiety, pallor and headache.

(i) Both adrenaline and noradrenaline, injected rapidly, intravenously, may cause a sudden marked increase in blood pressure, precipitating subarachnoid haemorrhage and occasionally hemiplegia. They can also cause ventricular arrhythmias including fatal ventricular fibrillation. In individuals with cardiac decompensation, adrenaline may precipitate acute pulmonary edema and hence, it should be administered with caution in the elderly and in patients with decompensated hearts.

Noradrenaline infusion has to be carefully controlled and blood pressure has to be checked at least every 15 minutes to prevent the above mentioned complications. *The infusion must never be left unattended.* Patients with myocardial infarction are more prone to develop arrhythmias during noradrenaline infusion and the drug has to be administered cautiously in this condition. Noradrenaline infusion, if stopped suddenly, may result in an alarming hypotension. The cause of this phenomenon is not known.

(ii) Adrenaline and noradrenaline (particularly the former) may produce anginal pain in persons with ischemic heart disease. Thyrotoxic or hypertensive individuals, and patients receiving rauwolfia alkaloids, ganglion blocking agents and M.A.O. inhibitors are more sensitive to the pressor effect of these drugs.

(iii) Noradrenaline infusion, if extravasated, may produce local vasospasm, necrosis, sloughing and gangrene.

Preparations and dosage :

(i) Adrenaline injection I.P., 0.5 or 1 ml. ampoules containing 1:1000 adrenaline (0.5 or 1 mg. in 0.5 or 1 ml. respectively) in water. Dose : 0.2 to 0.5 ml. by subcutaneous or intramuscular injection. The drug is rarely administered intravenously in the dose of 0.25 mg. diluted with saline and given slowly. Intracardiac route is employed

in certain emergencies.

(ii) Adrenaline inhalation U.S.P. is a nonsterile, aqueous solution of adrenaline tartrate.

(iii) Noradrenaline injection I.P. is a sterile 0.2 per cent solution of noradrenaline bitartrate available in 2 ml. ampoules. It is administered as an intravenous infusion. For this purpose, 2 ml. of noradrenaline bitartrate (equivalent to 8 mg. of the salt and 4 mg. of the base) is added to 1000 ml. of 5 per cent dextrose solution (which is generally acidic) resulting in a concentration of 4 µg of the base per ml. After judging the cardiovascular response with a test dose of 2 to 3 ml., the drug is administered at the rate of 0.5 to 1 ml. per minute. The dose has to be controlled according to the blood pressure response. *Noradrenaline is unstable at the neutral pH of normal saline and vitamin C (500-1000 mg) should be added to the infusion, if noradrenaline must be infused in normal saline.*

Therapeutic uses of adrenaline :

(a) *Allergic reactions* : Adrenaline is the drug of choice in the treatment of anaphylactic shock. For details see Chapter 20. It is life-saving in angioneurotic edema of the larynx.

(b) *Bronchial asthma* : Adrenaline, given subcutaneously or by inhalation is a potent drug in the treatment of an acute attack of bronchial asthma. (See Chapter 23)

(c) *Cardiac resuscitation* : Adrenaline is useful in treating sudden cardiac arrest due to drowning, electrocution, during Stokes-Adams syndrome and due to hypersensitive carotid sinus. Adrenaline, for obvious reasons, is more effective in syncope associated with ventricular standstill and is of little value if ventricular fibrillation is present. In the emergency treatment of cardiac arrest, various mechanical and electrical procedures to restore the circulation are of primary importance. However, these may fail to restore effective circulation. In such circumstances, adrenaline injected into the heart may be effective by the mechanical stimulus of the injection as well as by its inotropic cardiac action. It is usually given in the dose of 0.2 to 0.3 ml. of a 1 : 1000 solution through

a cardiac puncture, the most commonly used site being the fourth or fifth left intercostal space, 2 to 3 inches from the sternum. It must be emphasized that before injection, one must make sure by withdrawing blood into the syringe, that the tip of the needle is in a cardiac chamber and not in the cardiac wall. Injection of adrenaline into the heart muscle usually precipitates ventricular fibrillation which is totally resistant to correction. Under less pressing circumstances, adrenaline may be administered by intramuscular injection. In cases of complete heart block, isopropylarterenol is probably the drug of choice.

(d) *Control of haemorrhage*: Adrenaline in the concentration of 1 : 1000 to 1 : 20,000 is sometimes used topically for controlling bleeding from arterioles and capillaries. It is not effective against venous oozing or haemorrhage from larger vessels. Packs soaked in adrenaline solutions are commonly employed to control epistaxis and bleeding after tooth extraction.

(e) *Use with local anaesthetics*: Adrenaline, because of its vasoconstrictor effect, is used in the concentration of 1 : 20,000 to 1 : 100,000 along with local anaesthetics. Adrenaline reduces the systemic absorption of the local anaesthetic, thus prolonging its action and minimising its systemic toxicity.

Therapeutic uses of noradrenaline: Noradrenaline is mainly used for elevating the blood pressure in shock. The use of vasopressor agents in the treatment of shock is discussed in Chapter 28.

Routinely, alpha-receptor blocking drugs are used, for the control of the blood pressure, before and during operative removal of a pheochromocytoma. This antagonism of alpha receptor usually does not lead to irrecoverable hypotension after removal of the tumor. However, if there is a fall in blood pressure even after correction of hypovolemia, administration of noradrenaline may be useful.

ISOPROTERENOL (Isoprenaline, Isopropylarterenol): Isoproterenol is the most powerful,

synthetic, *beta-receptor stimulant* drug. Its action on alpha-receptors is very negligible.

Pharmacological actions: Its main actions are on the heart, smooth muscles and skeletal muscle vasculature.

Given intravenously in man, the drug lowers the peripheral vascular resistance in skeletal, renal and mesenteric vascular beds and produces a fall mainly in the diastolic pressure. This fall in blood pressure is antagonized by its powerful cardiac stimulant action. Hence, the systolic blood pressure may be raised or show only a negligible fall while the diastolic blood pressure is usually reduced. Routine therapeutic doses do not affect the pulmonary arterial pressure in man.

Isoproterenol, like adrenaline, relaxes the smooth muscles particularly those of bronchi and gastrointestinal tract. Its calorogenic and free fatty acid releasing actions are similar to those of adrenaline. It, however, causes less hyperglycemia.

Absorption, fate and excretion: Isoproterenol is inconsistently absorbed on sublingual or oral administration. Absorption is quicker after intramuscular injection and by inhalation. It is rapidly inactivated by uptake into tissue (uptake 2) and metabolised by COMT. Hence, its action is short lasting. Given orally it is less effective.

Adverse reactions: Depot preparation given sublingually can cause buccal ulceration. It is capable of producing palpitation, tachycardia, arrhythmias, anginal pain, headache and flushing. Combined isoproterenol-adrenaline administration in bronchial asthma may prove fatal. The drug has been demonstrated to produce myocardial necrosis in rats. The incidence of toxic manifestations is less with inhalation than after sublingual administration.

Preparations and dosage: Isoproterenol is a white, crystalline powder, soluble in water. Isoproterenol tablet I.P. contains 10 mg. of isopropylarterenol sulfate. Dose: 5 to 20 mg. sublingually.

Isoproterenol hydrochloride for inhalation is

available as 1 : 100 and 1 : 200 solutions in normal saline. Dose 0.5 ml. of 1 : 200 solution.

Therapeutic uses :

(a) *Bronchial asthma* : Isoproterenol is preferred by some to adrenaline in the treatment of an acute attack of bronchial asthma. (See Chapter 23).

(b) *Stokes-Adams syndrome* : Isoproterenol, because of its lesser liability to produce cardiac arrhythmias, is preferred to adrenaline in this condition. It may be administered intravenously or as sustained action tablets of 30 mg. by oral route in the dose of 60 to 120 mg. at 6 to 8 hourly intervals.

(c) *Shock* : Isoproterenol is sometimes being advocated as a cardiac stimulant in the treatment of bacteremic shock. The rationale of this use is discussed in Chapter 28.

Precautions and contraindications : Catecholamines should be administered cautiously in the presence of hypertension, hyperthyroidism and angina pectoris, and should be used carefully in hypotension during halothane, chloroform anaesthesia, and in acute left ventricular failure.

DOPAMINE (Intropin) : This naturally occurring precursor of noradrenaline acts on dopaminergic receptors. There are two types of dopamine post-synaptic receptors D1 and D2. Pre-synaptic receptors or autoreceptors for dopamine have also been demonstrated in the brain. It is also a weak alpha and beta adrenergic receptor agonist. It is metabolised by MAO and COMT.

Given in small doses (<5 mcg/kg/min.) by infusion in man, it causes renal, mesenteric and cerebral vasodilatation due to action on dopamine receptors. Slightly larger doses (5-10 mcg/kg/min.) maintain the effect on dopaminergic receptors and also activate beta adrenergic receptors. This causes increase in myocardial contractility, heart rate and cardiac output. This is an advantage in the treatment of shock. With doses between 10 and 20 mcg/kg/min., beta receptor action predominates. Larger doses (>20 mcg/kg/min.),

however, cause vasoconstriction, marked cardiac effect and decrease in renal blood flow. Dopamine does not cross the blood brain barrier.

It is given by slow intravenous drip, at the rate of 2.5 - 15 mcg/kg/min. In certain situations, the rate may be increased to 20 - 50 mcg/kg/min. It has been used in the treatment of shock, particularly cardiogenic and bacteremic shock.

Adverse reactions: These include nausea, vomiting, palpitation, ectopic beats and anginal pain. A sudden rise in blood pressure may occur. Small doses occasionally precipitate a fall in blood pressure. Infusion of large doses for long time may cause ischemia and gangrene of limbs.

Reduction in urine output, tachycardia and development of arrhythmias indicate toxicity. The drug has extremely short plasma half life and the effects usually disappear on stopping the infusion. If necessary, they can be countered by the use of the alpha blocker, phentolamine.

Dobutamine is a derivative of dopamine with selective inotropic effect, and negligible chronotropic and peripheral vascular actions. In patients with low-output cardiac failure, it increases the cardiac output without increasing the heart rate. Unlike dopamine, it does not cause renal vasodilatation. It is particularly useful in refractory, chronic, congestive, cardiac failure, unresponsive to digitalis. It may also have beneficial hemodynamic effects in patients with bacteremic shock. It has a short duration of action and is given by slow i.v. infusion in 5% dextrose, at the rate of 2.5 - 15 mcg/kg/minute. Its toxicity is similar to that of dopamine. Like other catecholamines, dobutamine loses its effect in an alkaline medium.

NONCATECHOLAMINES

The sympathomimetic amines devoid of the catechol nucleus comprise compounds like ephedrine, amphetamine and other vasopressors as well as smooth muscle relaxing compounds. These amines act (1) as partial agonists of noradrenaline and are capable of *directly stimulating* the adrenergic alpha or beta receptors. This ex-

plains the relaxation of the bronchial smooth muscle by ephedrine, uterine smooth muscle by isoxsuprine, vascular smooth muscle by nylidrine and stimulation of the myocardium by mephentermine, (2) by releasing noradrenaline and/or dopamine from the mobile pool within the chromaffin granules of the sympathetic neurones. This *indirect action* of the non-catecholamines produces effects mainly resembling those of externally administered noradrenaline.

These compounds are effective orally and are relatively resistant to monoamine oxidase action. Their action is, therefore, prolonged as compared to that of catecholamines. These drugs cross the blood brain barrier more easily and hence, have significant CNS effects.

EPHEDRINE is an alkaloid obtained from plants of the genus *ephedra*. The herb containing ephedrine, *ma huang*, has been employed in Chinese indigenous medicine for over 5000 years. Plants of this genus are commonly encountered in northern India and China.

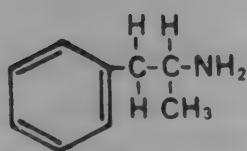
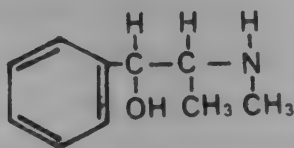


Fig. 14.5 : Amphetamine



Ephedrine

Pharmacological actions : Ephedrine stimulates both the alpha and beta adrenergic receptors and also releases noradrenaline from sympathetic nerve endings.

(i) **Cardiovascular actions :** Ephedrine increases blood pressure both by peripheral vasoconstriction and by increasing the cardiac output. Ephedrine increases the force of myocardial contraction but its action on the heart rate is variable. Repeated administration of ephedrine fails to elicit the same pressor response, the phenomenon being termed *tachyphylaxis*. The pressor effect of ephedrine is antagonized by the alpha receptor blocking agents but there is no significant reversal. Ephedrine is a much less potent pressor agent

than adrenaline but the pressor response persists for a longer time. Qualitatively, its actions on various blood vessels are similar to those of adrenaline.

(ii) **Smooth muscles :** Ephedrine relaxes the bronchial smooth muscle. The relaxation is less prompt than with adrenaline but persists for a longer time. Ephedrine also relaxes the uterine smooth muscle while it enhances the tone of trigone and the sphincter of the bladder.

(iii) **CNS actions :** Ephedrine stimulates the central nervous system probably by acting on the reticular activating system. In therapeutic doses, it often produces restlessness, insomnia, anxiety, tremors and increased mental activity. It enhances the monosynaptic and polysynaptic reflexes of the spinal cord and increases the depth and rate of respiration. Large doses may produce clonic convulsions.

(iv) **Eye :** Ephedrine produces mydriasis on local as well as systemic administration. Accommodation, intraocular tension and light reflex, however, are not affected.

(v) **Metabolic effects :** Ephedrine increases the metabolic rate and oxygen consumption. It is less effective than adrenaline in raising the blood sugar level.

Absorption, fate and excretion : Unlike the catecholamines, ephedrine is well absorbed on oral administration. It is relatively resistant to monoamine oxidase. It is deaminated to some extent in the liver and partly excreted as a conjugate. Approximately 60 to 75 per cent of the total administered dose is eliminated unchanged in urine.

Preparations and dosage :

(i) Ephedrine hydrochloride tablet I.P. contains 30 mg. of the salt. Dose : 15 to 60 mg. by mouth. For continuous medication, 30 mg. should be administered three or four times a day.

(ii) Ephedrine hydrochloride elixir contains 15 mg. of the salt per 5 ml. Dose : 5 to 10 ml. Ephedrine pediatric syrup N.F. containing 8 mg. of ephedrine hydrochloride per 5 ml. is also available. Dose : 5 ml. per year of age to a maximum of

20 ml. per dose 4 to 6 hourly.

(iii) Ephedrine hydrochloride injection contains 30 mg. of ephedrine hydrochloride per ml. Dose : 15 to 45 mg. by subcutaneous or intramuscular injection. Intravenous route is indicated only in emergencies.

(iv) Ephedrine nasal drops 1 per cent.

(v) Ephedrine eye drops contain 3 to 5 per cent ephedrine hydrochloride.

(vi) Pseudoephedrine hydrochloride (Sudafed): a stereoisomer of ephedrine available as 30 and 60 mg. tablets and syrup containing 30 mg. in 5 ml. and is used systemically as nasal decongestant.

Adverse reactions : The adverse reactions are similar to those encountered with catecholamines. Gastrointestinal upset, difficulty in micturition, insomnia, tremors and even psychotic symptoms with paranoid hallucinations have been reported after ephedrine. However, usually the drug is well tolerated. Precautions similar to those with catecholamines should be exercised during its administration.

Therapeutic uses :

(i) *Bronchial asthma* : Ephedrine is useful for preventing and treating chronic and moderately acute attacks. See Chapter 23.

(ii) *Nasal decongestion* : Ephedrine is administered as drops for nasal decongestion. However it may produce tachyphylaxis, after-congestion and systemic effects.

(iii) *Hypotension* : Ephedrine is employed intramuscularly to prevent or to treat hypotension during spinal anaesthesia.

(iv) *Stokes-Adams syndrome* : Ephedrine in the dose of 10-30 mg. 3 to 4 times daily, has been used to prevent ventricular asystole in Stokes-Adams syndrome. Isoprenaline is preferred to ephedrine for this purpose.

(v) *Mydriatic* : Ephedrine eye drops 3 to 5 per cent, are employed to produce mydriasis without cycloplegia. It is not useful in the presence of inflammation.

(vi) *In narcolepsy* : Because of its central stimulant effect, ephedrine has been claimed to be useful in narcolepsy. Amphetamine, however, is

superior to ephedrine in this respect.

(vii) *Miscellaneous* : Ephedrine has been used with varying success in urinary incontinence and nocturnal enuresis. It is of some value in relieving paroxysms of whooping cough and reducing the pain of dysmenorrhoea. It is sometimes used in the treatment of urticaria. Ephedrine is used in the dose of 10-30 mg. several times a day, as an adjuvant to the anticholinesterases in the treatment of myasthenia gravis.

AMPHETAMINE, which bears a close structural similarity to ephedrine is available in the racemic and the dextro forms. The d-isomer is approximately 3 to 4 times as potent as the levo form in its central effects while the levo form is slightly more potent than the dextro form in its effects on the cardiovascular system (Fig. 14.5).

Pharmacological actions :

(i) *Cardiovascular effects* : Amphetamine increases the systolic and diastolic blood pressure. The action on the heart rate is variable. Amphetamine does not elevate the cardiac output significantly. Tachyphylaxis to the hypertensive effect of amphetamine is known.

(ii) *CNS actions* : Amphetamine is a potent central nervous system stimulant like caffeine. It produces a variety of psychic effects such as increased mental and physical activity, elation, euphoria or dysphoria, insomnia, tremors, restlessness, confusion, agitation and headache. In therapeutic doses (10-30 mg. orally), amphetamine produces wakefulness, postpones fatigue and improves the physical performance. These psychic effects of amphetamine are determined by the personality of the individual as well as the dose.

In doses more than 30 mg. amphetamine stimulates the medullary respiratory centre, increasing the rate and depth of respiration and acts as an analeptic.

The psychic effects of amphetamine are attributed to cortical stimulation while stimulation of the reticular activating system probably accounts for its analeptic effect.

Repeated and excessive stimulation by am-

phetamine is usually followed by fatigue and depression.

(iii) **Smooth muscles:** It contracts the sphincter of the bladder and relaxes the bronchial smooth muscle only in large doses. The actions on other smooth muscles are variable.

(iv) **Appetite suppressant :** Amphetamine reduces appetite probably by acting on the lateral hypothalamic area concerned with feeding. It has little effect on food intake in persons with compulsive overeating due to psychic disturbances.

(v) **Miscellaneous effects:** Amphetamine has a moderate anticonvulsant activity and is useful in petit mal seizures. Instilled into the eye, it can produce mydriasis.

Absorption, fate and excretion: Amphetamine is well absorbed on oral and parenteral administration. The effect appears within 30 minutes after oral and 5 minutes after subcutaneous administration. Like ephedrine, it is relatively resistant to inactivation by monoamine oxidase. Approximately 40 per cent of the total administered dose of amphetamine is excreted unchanged in urine. The metabolism of the remainder is not clearly elucidated.

Adverse reactions : In addition to effects like palpitation, restlessness, headache, tremors and agitation due to sympathetic stimulation, amphetamine can often produce marked anxiety, confusion, erratic behaviour, paranoid psychosis, visual hallucinations and misperception. This fact and the danger of after-depression and dependence should discourage the use of this compound by students during examination periods.

Angina, delirium, acute neurotic or psychotic episodes, suicidal and homicidal tendencies and circulatory collapse are known to develop following ingestion of a large dose. Hyperpyrexia often accompanies the circulatory collapse in acute amphetamine intoxication. Cardiac arrhythmias, flushing, pallor, hypertension and excessive sweating have also been described. Dry mouth, anorexia, nausea, vomiting, abdominal cramps and diarrhoea are sometimes encountered. Death is usually due to convulsions and coma. Treatment of acute intoxication is entirely sympto-

matic. Sedation with chlorpromazine is indicated to control the excessive central stimulation. Guanethidine and alpha adrenergic receptor blocking agents such as phentolamine are employed to control hypertension. The urine should be acidified to promote the excretion of amphetamine. Peritoneal dialysis may prove useful for removing circulating amphetamine. Individuals on therapy with monoamine oxidase inhibitors may develop an alarming rise in blood pressure with therapeutic doses of amphetamine.

Amphetamine causes drug dependence which is mainly psychic. With habituation, tolerance to the drug may appear. Central nervous system tolerance to amphetamine may be partly due to depletion of noradrenaline and partly because of development of a false neurotransmitter p-hydroxy-norephedrine. Psychic disturbances are marked in an addict and drug withdrawal produces fatigue, tremor, depression and gastrointestinal disturbances. However, a serious withdrawal syndrome is rare.

Preparations and dosage: Amphetamine sulfate I.P. is available as tablets containing 5 mg. of the salt. Dose : 5 to 10 mg. given orally in the morning and at midday. Dextroamphetamine sulfate I.P. is available as 5 mg tablets and is administered in similar doses as amphetamine.

Therapeutic uses : Amphetamine and dextroamphetamine (Dexedrine) are mainly employed for their central effects in :

(i) **Narcolepsy :** Amphetamine in the doses of 30 to 40 mg. per day in divided doses improves narcolepsy and prevents attacks of sleep. The drug should not be administered after 4 p.m. as it interferes with natural sleep.

(ii) **Obesity :** Amphetamine and dextroamphetamine by virtue of their anorexiant effect are employed to reduce the food intake in obese people. They have, however, many disadvantages. For details see Chapter 36.

(iii) **Miscellaneous :** d-Amphetamine may control certain cases of epilepsy usually those with temporal lobe epilepsy exhibiting aggressive behaviour. It is useful in aborting seizures in certain cases of nocturnal epilepsy and in the

management of the *hyperkinetic syndrome*.

Amphetamine is of some value in certain behavioural problems in children with abnormal EEG. These children are usually hyperexcitable and hyperkinetic. They can be managed by dextroamphetamine in dose of 2.5-5 mg. twice daily. The treatment is usually not necessary after 5 years of age. *The drug may have a deleterious effect in children with psychopathic personalities.*

Since better drugs are now available, amphetamine should not be used as an antidepressant, an antifatigue agent, appetite suppressant, a pressor agent nor in the treatment of dysmenorrhoea, migraine or parkinsonism.

NONCATECHOLAMINES MAINLY USED AS VASOPRESSOR AGENTS

The vasopressor sympathomimetic amines are employed to correct hypotension due to cardiogenic shock and to prevent and treat hypotension due to neurogenic shock, e.g. during or after spinal anaesthesia. In addition, these agents are also useful in correcting cardiac arrhythmias associated with hypotension and in the treatment of paroxysmal atrial tachycardia, as some of these agents increase the vagal tone reflexly. They are, however, of little value in the treatment of late haemorrhagic or bacteremic shock. The requirements of an ideal vasopressor agent are:

(1) It must raise the arterial blood pressure upto or near the lower limits of normal for the patient. The rise of blood pressure should be prompt, predictable and easily controllable.

(2) It should not produce constriction of the vital blood vessels like the coronary, cerebral and renal arteries.

(3) It should not produce myocardial or central stimulation, tachycardia or cardiac arrhythmias, tachyphylaxis and local irritation. Needless to say, no drug fulfils all these requirements.

The vasopressor agents increase the blood pressure either by increasing the total peripheral resistance or by augmenting cardiac output or by a combination of both these mechanisms. Opinion is divided regarding the superiority of one type

of vasopressor agent over the other. These agents are routinely administered by parenteral route. It is customary to administer a fraction of the total dose intravenously and the remainder by intramuscular injection.

When using vasopressor agents, the blood pressure should be raised only moderately above the critical levels (100/70 mm. Hg.) necessary for adequate tissue perfusion. An exaggerated vasoconstriction jeopardizes tissue perfusion and defeats the very purpose of vasopressor therapy. Tachyphylaxis to certain vasopressors may develop rarely necessitating a change-over to another drug; however, *other causes of refractoriness to vasopressors like hypovolemia and metabolic acidosis should be ruled out before changing over to another agent.*

The use of noradrenaline and dopamine for raising the blood-pressure has been discussed earlier.

The other important vasopressor agents are :

METARAMINOL (Aramine): Metaraminol resembles noradrenaline in pharmacological actions except that it is less potent and has a more gradual onset and longer duration of action. It raises blood pressure mainly by peripheral vasoconstriction. Rise in blood pressure is usually accompanied by bradycardia. Metaraminol increases the cardiac output, cardiac metabolism and the force of ventricular contraction. It increases the coronary blood flow, probably as a result of increased blood pressure, and reduces the cerebral, splanchnic, renal and limb blood flow. Metaraminol tends to raise the pulmonary artery pressure probably by direct constriction of pulmonary vessels. The drug has no effect on the central nervous system. The pressor effect lasts for about 1½ hour after a 5 mg intramuscular dose. The drug is used in the treatment of hypotension.

Metaraminol is administered intramuscularly in the dose of 2 to 10 mg. The intravenous dose is 0.5 to 10 mg. Alternatively, 100-200 mg. of the drug can be given as a slow infusion in 500 ml of 5 per cent glucose. It can also be used as a nasal decongestant.

PHENYLEPHRINE (Neo-synephrine): This vasopressor agent has a powerful α receptor stimulant action. The pressor response is accompanied by bradycardia owing to reflex vagal stimulation. The pulmonary artery pressure falls due to a decrease in the pulmonary blood flow. It is devoid of action on the C.N.S.

Phenylephrine is administered by subcutaneous or intramuscular injection, or intravenously in the dose of 5-10 mg. and 0.5 mg., respectively. The pressor effect of a single subcutaneous dose persists for 45 to 50 minutes while that of the intravenous dose lasts for 15 to 20 minutes. Alternatively, 10 mg. of the drug may be administered slowly through 500 ml. of saline drip. Its absorption from the gut is unreliable. It is mainly used as a nasal decongestant and a mydriatic (1-2 per cent)

In addition, the drug is useful in the treatment of paroxysmal atrial tachycardia.

METHOXAMINE (Vasoxine) : Methoxamine raises blood pressure purely by vasoconstrictor effect. Peripheral vasoconstriction is accompanied by pilomotor stimulation. Its haemodynamic actions are similar to those of phenylephrine. It is devoid of myocardial stimulant (β receptor) activity. It has also been employed in the treatment of paroxysmal atrial tachycardia. The intramuscular dose is 10 to 20 mg. and the intravenous dose is 5 to 10 mg. The drug can be administered as an intravenous infusion in the concentration of 60 mg. in 500 ml. of glucose saline. A 0.25 per cent solution is used as a nasal decongestant.

NASAL DECONGESTANTS

In addition to some of the vasopressor agents mentioned above, many other sympathomimetic amines can be used topically as nasal decongestants. An ideal nasal decongestant should produce a prompt, prolonged and reliable effect and should be free from tachyphylaxis, local irritation and damaging effect on nasal cilia. It should not

produce after-congestion and systemic adverse effects. Unfortunately, only a few drugs in very dilute solution are safe; majority of them can produce a temporary or even permanent damage to ciliated respiratory epithelium, with the possibility of further atrophic changes. Some of these drugs also produce *rhinitis medicamentosa* and rebound vasodilatation resulting in more distressing nasal symptoms than were initially present.

Combinations of decongestants with antihistaminics, corticosteroids and antibiotics are available for local use but their efficacy is very doubtful; the majority of such solutions are wasteful and may even be dangerous.

Nasal solutions are useful in nasal allergy, acute rhinitis or sinusitis, acute otitis media with eustachian obstruction and sinus headaches. Solutions for nasal application are best used as fine sprays or douches rather than drops. Therapeutically, they are only palliative, and by themselves are not curative.

In many cases simple decongestion is all that is required and ephedrine hydrochloride 0.5 per cent in normal saline is satisfactory for this purpose. Xylometazoline hydrochloride 0.1 per cent (Otrivin), 2 amino heptane sulfate 1 per cent (Tuamine sulfate) and oxymetazoline 0.05% (Nasivion) produce similar effects, at a higher cost; only the duration of action may differ.

Propylhexadrine by inhalation (Benzedrex) has actions similar to amphetamine but does not stimulate the central nervous system

SELECTIVE β_2 RECEPTOR STIMULANTS

As mentioned earlier, isoprenaline acts by stimulating β receptors and, therefore when used in bronchial asthma may cause adverse cardiac effects. Recently, drugs with predominant action on β_2 receptors have become available. These are orciprenaline (metaproterenol), salbutamol, terbutaline, albuterol, ritodrine and isoetharine. Given by inhalation, they act as promptly as isoprenaline but have a longer duration of action (2-4 hours) with much less stimu-

lant action on the heart. Adverse effects are similar to those of isoprenaline though they are less severe. Among the various drugs available, none appears to be clinically superior to salbutamol (See Chapter 23).

Salbutamol, orciprenaline and ritodrine have also been used effectively as uterine smooth muscle relaxants to delay delivery in premature labour. (See Chapter 40)

XAMOTEROL: This new synthetic drug has selective beta 1 - adrenoreceptor partial agonist properties. Given orally, it has about half the beta-receptor stimulating activity of a full agonist such as nor-adrenaline. Thus, at rest when sympathetic tone is low, it exerts a moderate inotropic effect; however when it is high or during exercise, the drug partially antagonises the beta-adrenergic response. Thus, it is believed that xamoterol by exerting both agonist and antagonist effects, stabilizes the beta-receptor at approximately the level of its own intrinsic sympathomimetic activity.

Given in the dose of 200 mg twice daily in patients with CCF, xamoterol improves myocardial contractility at rest by improving the ventricular function. The myocardial (diastolic) relaxation is enhanced and cardiac index is increased. During submaximal exercise, the cardiac output is maintained, but the increase in heart rate is blunted. Interestingly, these hemodynamic changes appear to be achieved, without any increase in resting myocardial oxygen consumption. Along with the improvement in the pumping function of the heart, the drug also causes symptomatic improvement.

At present, the drug has been reported to be useful in patients with mild to moderate heart failure due to ischaemic heart disease. Patients with severe heart failure, with resting (sinus) heart rate over 90/min. or those with high daily diuretic requirement (furosemide 80 mg or more) are not likely to be benefited by this drug; in fact, such patients may deteriorate due to its sympathetic antagonistic action. It may also be useful in patients with auricular fibrillation and CCF, as ad-

junct to digoxin therapy.

The drug is well tolerated and toxicity reported so far is mild. It should not be given to patient with asthma or COPD.

ANORECTIC SYMPATHOMIMETIC DRUGS

As described earlier, amphetamine has an appetite suppressant (anorectic) action. Various drugs claimed to have similar anorectic action with less marked CNS stimulation are now available. These include phenteramine, chlorphenteramine, fenfluramine and phendimetrazine. The use of such agents in the treatment of obesity is discussed in Chapter 36.

MISCELLANEOUS COMPOUNDS

NYLIDRIN (Arlidin) : Nylidrin, a beta receptor stimulant, has been advocated in the treatment of peripheral vascular diseases. Its therapeutic usefulness is controversial.

ISOXSUPRINE HYDROCHLORIDE (Duvadilan): This has similar beta receptor actions as nylidrin as well as direct action. It has a potent inhibitory effect on vascular and uterine smooth muscle, both *in vivo* and *in vitro*, and has been demonstrated to produce some increase in the blood flow of resting uterine muscle. On this basis, the drug has been recommended in the treatment of dysmenorrhoea, threatened abortion, premature labour and peripheral vascular diseases. However, there is no convincing evidence that the drug is useful in vasospastic disorders. As with other commonly used vasodilators the increase in muscle blood flow is much smaller than that which accompanies moderate exercise. The drug can cause nausea, vomiting, palpitation,

nervousness and trembling. It is available as tablets containing 10 mg. of the drug and injections for I.M. and I.V. use. Orally, it is used as a vasodilator in the dose of 80 mg. per day in divided doses, whereas injections are used in the treatment of premature labour.

SYMPATHETIC BLOCKING DRUGS

The actions produced by stimulation of the sympathetic nervous system can be blocked peripherally by drugs acting in various ways. These blocking agents can be classified into:

I. Drugs that induce depletion of catecholamines from the various body tissues e.g. reserpine and tetrabenazine (see Chapter 26).

II. Drugs postulated to interfere with synthesis of the adrenergic transmitter either in the adrenergic neurone or in the adrenal medulla e.g. alpha methyl dopa, alpha methyl para tyrosine (see Chapter 26).

III. Drugs that interfere with transmission of impulses across the postganglionic adrenergic neurones e.g. adrenergic neurone blocking agents like guanethidine (see Chapter 26).

IV. Drugs which block the adrenergic receptors without interfering with either the synthesis and/or release of adrenergic neurohumoral transmitter, e.g. alpha and beta adrenergic blocking agents.

ADRENERGIC BLOCKING AGENTS

Adrenergic blocking agents prevent the response of effector organs to endogenous as well as exogenous adrenaline and noradrenaline. These drugs block either alpha or beta adrenergic receptors.

ALPHA RECEPTOR BLOCKING AGENTS: These drugs are more effective in antagonising the alpha receptor effects of exogenously administered adrenaline and noradre-

naline than those following adrenergic stimulation. They are chemically classified into:

(a) Beta haloalkylamines e.g. dibenamine and phenoxybenzamine.

(b) Natural and dihydrogenated ergot alkaloids.

(c) Imidazoline derivative e.g. tolazoline and phentolamine.

(d) Miscellaneous: prazosin, yohimbine, and chlorpromazine.

(a) **DIBENAMINE AND PHENOXYBENZAMINE (Dibenzyline):** The receptor blockade produced by these agents is remarkably prolonged and stable and in the later stages, it is not altered by increasing the concentration of the catecholamines at the receptor sites. The blockade is, therefore, referred to as non-equilibrium type of blockade, loosely termed as 'irreversible blockade'. Phenoxybenzamine is a fairly potent antihistaminic.

The adrenergic blocking activity of phenoxybenzamine is 6 to 10 times more than that of dibenamine.

Pharmacological actions : The adrenergic blockade produced by these agents is established only after 1 to 2 hours even on intravenous administration and persists for 3 to 4 days. The usual blocking doses do not affect the blood pressure significantly in normal individuals beyond a slight lowering of diastolic blood pressure but significant hypotension usually results in persons with pheochromocytoma. The compounds evoke Dale's vasomotor reversal. They do not antagonize the cardiac actions of catecholamines but are capable of inhibiting cardiac arrhythmias induced by adrenaline and sympathomimetic amines in both normal individuals and in patients under chloroform, cyclopropane or halothane anaesthesia. It must be emphasised that these agents *can prevent but cannot reverse* such arrhythmias.

The alkylamines antagonize the mydriatic effect of adrenaline and produce miosis.

In clinically effective doses, phenoxybenzamine causes orthostatic hypotension and reflex

tachycardia in most patients. Phenoxybenzamine, on slow intravenous infusion, often produces sedation and drowsiness, probably by its antihistaminic activity while large doses of both dibenamine and phenoxybenzamine often produce nausea, vomiting, increased excitability and even convulsions. The metabolic effects of catecholamines are blocked to varying extent in different species. However, they have no significant effect on the motility of the gastrointestinal tract.

Absorption, fate and excretion: Given orally, the absorption of haloalkylamines is irregular; phenoxybenzamine is absorbed better than dibenamine. The drugs may produce irritation on subcutaneous or intramuscular administration and hence, are administered by mouth or by intravenous route. Because of their high lipid solubility, these compounds tend to accumulate in the body fat depots from which they are released slowly. Approximately 50 per cent of the intravenously administered dose of phenoxybenzamine is excreted within 12 hours and 80 per cent is eliminated within 24 hours.

Adverse reactions : Besides miosis, dryness of mouth, nasal stuffiness and inhibition of ejaculation, the compounds may produce palpitation, giddiness and postural hypotension. Central effects including lethargy, fatigue, nausea and vomiting have been reported. The drugs are capable of producing cumulative toxicity.

Preparations and dosage : Dibenamine is no longer used in therapeutics.

Phenoxybenzamine (Dibenzylamine) is available as 10 mg capsules. The usual daily maintenance dose is 20-60 mg. It has been used orally in the long term treatment of patients with pheochromocytoma who are not suitable for surgery.

(b) **NATURAL AND DIHYDROGENATED ERGOT ALKALOIDS:** The chemistry of the ergot alkaloids is discussed elsewhere. The natural amino acid ergot alkaloids, ergotamine, ergosine, ergocornine, ergocristine and ergocryptine (the last three collectively termed formerly as "ergotoxine") and their dihydrogenated deriva-

tives can block the alpha adrenergic receptors. The blockade is of shorter duration than that caused by haloalkylamines. The amine ergot alkaloid, ergometrine, is devoid of adrenergic blocking activity and is discussed in Chapter 40. The amino acid ergot alkaloids and their dihydrogenated derivatives, in addition, have a direct stimulant effect on the smooth muscle; thus, they cause contraction of uterine musculature and blood vessels. The stimulant activity on the smooth muscle decreases from the natural amino acid alkaloids to their dihydrogenated derivatives with a corresponding increase in the alpha adrenergic blockade. Thus, the natural amino acid alkaloids usually raise the blood pressure and may constrict coronary vessels. The dihydrogenated alkaloids, on the other hand, have a minimal constricting effect on coronaries and usually produce hypotension, more so in hypertensive individuals, by a combination of alpha adrenergic blockade and depression of the vasomotor centre. The exception to this is dihydroergotamine which retains a considerable vasoconstrictor effect in addition to adrenergic blocking activity. It has been used to treat orthostatic hypotension due to autonomic neuropathy. Ergot alkaloids also reduce the sympathetic tone by depression of the vasomotor centre, induce bradycardia by central vagal stimulation and direct myocardial depression and may cause vomiting by stimulation of the chemoreceptor trigger zone.

Actions of the ergot alkaloids on the uterus are discussed in Chapter 40.

Absorption, fate and excretion : The amino acid alkaloids and their dihydrogenated derivatives are poorly absorbed on oral administration. A part of the total parenteral dose is degraded in the body.

Adverse reactions: These compounds often produce nausea, vomiting, miosis and postural hypotension. Anginal pain may occur particularly with natural amino acid alkaloids due to coronary constriction. The natural alkaloids, on prolonged administration, may also induce paraesthesiae, tingling, numbness and occasion-

ally frank gangrene due to peripheral vasospasm. Headache, diarrhoea, confusion, depression, drowsiness and rarely hemiplegia and cerebral haemorrhage have also been reported with ergotamine.

Preparations and dosage:

(i) Ergotamine tablet I.P. contains 1 mg. of ergotamine tartrate. Dose : 1 to 2 mg. as a single dose by mouth, 3 to 4 mg. sublingually.

(ii) Ergotamine injection I.P. contains 0.5 mg. of ergotamine tartrate in one ml. of water. Dose : 0.25 to 0.5 mg by subcutaneous or intramuscular injection.

(iii) Dihydroergotamine injection (D.H.E.) : Dose : 1 to 1.5 mg by subcutaneous or intramuscular injection.

(iv) D.H.E. tablets : Upto 20 mg/day, in divided doses, to treat orthostatic hypotension due to autonomic neuropathy.

(v) Hydergine : See Chapter 26.

(c) **IMIDAZOLINE DERIVATIVES:** The compounds tolazoline (Priscoline) and phentolamine (Regitine), in addition to alpha adrenergic blockade, produce an increase in the force of contraction of myocardium and tachycardia. They produce dilatation of the peripheral blood vessels, particularly the arterioles and capillaries of the skin, and increase the motility of the gut and the secretion of hydrochloric acid. The salivary, lacrimal, respiratory and pancreatic secretions are also augmented. The compounds also exert a mild anti-5-HT activity.

Tolazoline, because of its predominant cardiac effect, often evokes a mild rise in blood pressure while phentolamine usually produces a moderate fall due to peripheral vasodilatation.

Absorption, fate and excretion: Tolazoline is well absorbed on oral and parenteral administration and eliminated mainly unchanged in urine. Phentolamine is poorly absorbed on oral administration; approximately 1/10th of its total parenteral dose is eliminated in urine while the rest is probably metabolized.

Adverse reactions : These include palpita-

tion, flushing and apprehension. Other disturbances are a sensation of coldness, postural hypotension, piloerection, nausea, vomiting, epigastric distress and diarrhoea. Excessive doses of tolazoline may induce profuse sweating. It also occasionally produces severe hypertension, may precipitate myocardial infarction and activate peptic ulcer.

Preparations and dosage:

(i) Tolazoline tablets I.P. contain 25 mg. of tolazoline hydrochloride. Dose : 25 to 75 mg., by mouth.

(ii) Tolazoline injection N.F. contains 25 mg. per ml. of tolazoline hydrochloride in water. Dose : 50 mg. 2 to 4 times a day by subcutaneous or intramuscular injection.

(iii) Phentolamine hydrochloride 50 mg tablets.

(iv) Phentolamine mesylate injection contains 5 mg. of the drug per ml. Dose : 5 mg. intramuscularly or intravenously.

(d) MISCELLANEOUS :

PRAZOSIN (Minipress): This drug acts by blocking alpha receptors selectively. It dilates both arteries and veins, causing reduction in venous return and cardiac output. It is used to treat essential hypertension (see Chapter 26).

YOHIMBINE, an alkaloid from the West African tree *Yohimbene*, produces a competitive blockade of alpha receptors which persists only for a short time. The drug enjoys a reputation as an aphrodisiac and is claimed to help 50% of people with impotence. However, prolonged therapy is needed.

Alpha adrenergic blocking action of chlorpromazine and haloperidol is discussed in Chapter 11.

Therapeutic uses of alpha adrenergic blocking agents: These drugs have limited therapeutic applications, mainly owing to their toxicity like tachycardia and postural hypotension. The important therapeutic uses are:

(i) **Peripheral vascular disease:** Phenoxybenzamine, hydergine, tolazoline and

azapetine have been tried in the treatment of peripheral vascular disorders. The value of these agents in the treatment of occlusive peripheral arterial diseases like arteriosclerosis obliterans and thrombo-angitis obliterans remains highly controversial. They are, however, useful in Raynaud's syndrome. Phentolamine infiltrated in the dose of 2.5 to 5 mg. prevents cutaneous necrosis due to extravasation of noradrenaline.

(ii) **Hypertension and pheochromocytoma:** See Chapter 26.

(iii) **Shock :** These drugs have been shown to be useful in the treatment of shock due to infection and myocardial failure. (See Chapter 28).

BETA ADRENERGIC BLOCKING AGENTS: These drugs selectively and competitively block the actions of catecholamines mediated through beta-receptor stimulation. Thus, the beta-receptor stimulating actions of adrenaline and isoproterenol are blocked but positive chronotropic effects of calcium, barium, theophylline and digitalis are not affected. At the cellular level, the drugs inhibit the activity of the membrane enzyme adenylyl cyclase and thus decrease the production of cyclic AMP. Apart from this common property, some of the compounds also have other pharmacological actions.

The important beta-adrenergic blocking agents can be classified as:

I. Specific beta-blockers e.g. Sotalol, Timolol, Nadolol.

II. Beta-blockers with 'membrane stabilizing activity' and 'intrinsic sympathomimetic property' e.g. Oxprenolol (Trasicor), Alprenolol and Pindolol.

III. Beta-blockers with membrane stabilizing activity e.g. Propranolol.

IV. Beta-blockers with cardioselective action e.g. Acebutolol, Atenolol and Metoprolol. Of these, acebutolol also has intrinsic sympathomimetic activity.

V. Beta-blockers with additional alpha blocking property e.g. Labetalol.

Pharmacological Actions :

(a) *Effects of beta-blockade:* These drugs do

not produce any marked effect on the normal heart in the subject at rest. In the presence of increased sympathetic tone, however, the beta-blockade in the heart prevents a rise in heart rate, cardiac output and stroke work. There is a reduction in myocardial contractility. The automaticity is suppressed and the atrioventricular (AV) conduction is slowed. The cardiac response to exercise and to other situations in which sympathetic tone is increased, is attenuated. These drugs usually reduce myocardial oxygen requirements and improve exercise tolerance in patients with angina.

Beta-blockers also reduce blood pressure probably by their action on the heart and reduction in cardiac output. They lower the plasma renin activity and also have a central hypotensive action. Although these drugs may enhance the pressor effects of adrenaline, the vascular action appears to be of less clinical importance in the absence of high levels of circulating catecholamines.

The blockade of beta-receptor sites in bronchi and bronchioles causes increase in airway resistance which could be dangerous in patients with asthma. Other effects include prevention of adrenaline-induced glycogenolysis in the skeletal muscle and inhibition of the release of free fatty acids from the adipose tissue. Certain beta-blockers are more cardioselective in action than others.

(b) *Membrane-stabilizing action* (See Chapter 12) : Propranolol and some other beta-blockers have a direct depressant effect on the heart similar to that of quinidine. This membrane effect is unrelated to beta-blocking potency and occurs only with high concentrations of the drug. Hence, it is not relevant to the clinical use of beta blockers nor does it affect the choice of a beta blocker.

(c) *Intrinsic sympathomimetic-action:* Some of the beta-blockers possess beta-receptor stimulating activity (partial agonist property). It has been suggested but not proved, that beta-blocking agents with additional intrinsic sympathomimetic activity may cause less myocardial depression and are thus less likely to precipitate congestive cardiac failure in the presence of damaged heart.

Pindolol and oxprenolol which have partial agonistic activity in the doses used for beta-blockade may not impair A-V conduction.

It should be noted that the pharmacological actions of beta-receptor antagonism are always present at lower concentrations of the drug than either membrane stabilizing or paradoxical agonist effect. *The primary beta-blocking action of all these drugs is in fact mostly responsible for their beneficial as well as adverse effects.*

(d) *Effects on the central nervous system* : Highly lipid soluble propranolol readily crosses the blood-brain barrier and has sedative and anti-convulsant effects in laboratory animals. This action is unrelated to beta-blockade. In man, propranolol alters mood and has been tried in psychiatric disorders. Various beta-blockers, however, differ in their ability to cross the blood brain barrier and in their consequent actions on the CNS. Thus atenolol probably does not cross the blood brain barrier at all.

(e) *Metabolic effects* : Beta-blockers are capable of modifying the carbohydrate and lipid metabolism. Such effects are complex and variable and their clinical significance is not yet well defined.

(f) *Intraocular pressure*: β -blockers, when used topically or orally, are known to cause a

reduction in intraocular pressure. The mechanism of action is not known.

Absorption, fate and excretion: The effective oral dose ranges of various β -blocking drugs are wide. Plasma concentrations vary markedly between individuals receiving the same dose. This is because although most of these compounds are completely and rapidly absorbed orally, some of them like propranolol, alprenolol and metoprolol are rapidly metabolized almost entirely by the liver. Because of such hepatic metabolism during their first passage through the liver, a part of the oral dose fails to reach the peripheral circulation. Thus for propranolol and alprenolol, the relative oral bio-availability is low and variations in plasma levels are marked (almost upto 20 fold), depending upon the extent of hepatic inactivation during the first pass. Practolol is largely excreted unchanged by the kidney while pindolol, acebutolol, atenolol and timolol are eliminated to variable extents by both routes. Because of this, the relative oral bioavailability of pindolol, practolol and sotalol is better and variations in plasma levels are much less marked. The plasma half life of the beta-blocking drugs that are mostly metabolized by the liver is short (2-3 hours), whereas that of drugs like practolol which are mainly excreted unchanged by the kidneys is

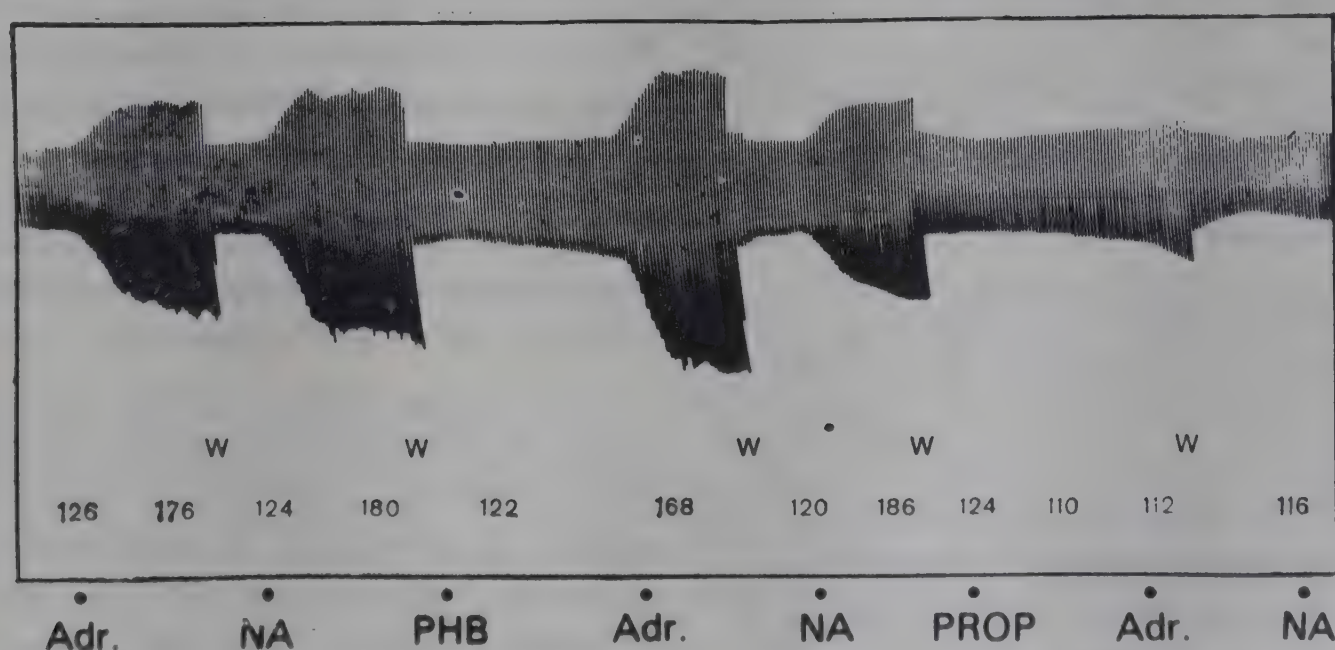


Fig. 14.5 : Effects of alpha adrenergic blocking agent phenoxybenzamine (PHB) and beta adrenergic blocking agent propranolol (PROP) on the actions of adrenaline and noradrenaline on isolated rabbit auricle. Note the reduction in the rate and the amplitude of auricular contraction with PROP in contrast to phenoxybenzamine.

Table 14.3 : Properties of some beta-adrenergic blocking drugs

Drugs	Cardio selectivity	Partial agonist activity	Protein binding %	Liver metabolism	Kidney excretion	Plasma half-life (hrs)
Propranolol (Inderal, Cliplar)	No	0	93	+++	+	3-6
Oxprenolol (Trasicor)	No	++	—	+++	+	1-2
Pindolol (Visken)	No	+	51	++	++	3-4
Sotalol (Beta-cardone)	No	0	54	+	+++	5-12
Alprenolol	No	++	85	+++	+	2-3
Nadolol (Corgard)	No	0	—	±	++++	20-24
Acebutolol (Sectral)	Yes	+	84	+	+++	3-10
Atenolol (Tenormin)	Yes	0	<5	+	+++	6-8
Metoprolol (Lopresor)	Yes	0	12	+++	+	3-6
Timolol (Betim)	No	±	—	++	++	4-6
Labetalol *	No	0	50	+++	+	4-5

* Alpha receptor blocking property; Present +; Absent 0; No information available —

longer (8-12 hours). Plasma half life is also modified by disease of the liver and of the kidney (Table 14.3). The plasma half life, however, does not correlate well with the duration of the therapeutic effects of betablockers, which is relatively long lasting. This is because the plasma level declines exponentially, thus following first order kinetics while the effect decreases linearly, following zero order kinetics. Hence, most preparations can be given orally at much longer intervals than is suggested by their plasma half-lives.

Adverse reactions : These are mostly due to the extended pharmacological actions. Thus, propranolol may cause sudden hypotension and pronounced bradycardia leading to cardiac asystole. The ventricular function depends on increased contractility due to sympathetic activity and beta-blockade prevents this homeostatic response leading to clinical heart failure. Congestive cardiac failure is thus the most important severe adverse effect of β -blockers. Because of their action on A - V conduction, some of these

drugs can aggravate A - V conduction defects. Hence, they are contraindicated in the presence of serious A - V conduction disturbances. However, this action may be beneficial in patients with atrial fibrillation resistant to digitalis. Beta-blockers with additional 'quinidine like activity' may cause a direct depression of the damaged heart leading to myocardial failure.

If propranolol therapy is to be discontinued in angina, the dosage should be reduced gradually, as myocardial infarction may be precipitated following its abrupt withdrawal.

Other adverse effects include constipation, nausea, vomiting, bronchospasm particularly in patients with bronchial asthma. These drugs prevent the correction of hypoglycemia by adrenergic body mechanisms ('hypoglycemia unresponsiveness') and aggravate neuroglycopenic symptoms of hypoglycemia.

Cold extremities and absent pulses may sometimes be observed after beta-blockade. Raynaud's

phenomenon may occasionally be troublesome and intermittent claudication may be aggravated.

Prolonged use of propranolol can cause fatigue, muscle cramps, lethargy and rarely mental depression and hallucinations. Peripheral neuropathy has also been reported. Miscellaneous reactions include allergic reactions, thrombocytopenia and agranulocytosis. These are rare.

Isoprenaline is the rational antagonist and should be administered to treat the toxicity due to beta-blockers.

Table 14.4 shows the dosage schedules of the commonly used beta adrenergic blocking drugs.

Table 14.4 : Doses of some beta adrenergic blocking drugs

	Totally daily Dose (mg)	Schedule
Propranolol	80-240	6 - 12 hourly
Metoprolol	100-400	12 hourly/single
Atenolol	50-100	Daily
Timolol	10-40	12 hourly
Pindolol	20-60	6 hourly

Therapeutic uses:

Clinically, in terms of beta blocking activity, no single drug is demonstrably superior to others. The choice is then guided by safety, other pharmacological properties, ease of administration and cost. In the presence of airway obstruction or peripheral vascular disease, a cardioselective beta-blocker may be chosen, keeping in mind that cardioselectivity is not absolute. The therapeutic uses of beta blockers are :

(i) **Angina pectoris** : Betablockers are the mainstay of the chronic, prophylactic treatment of patients with angina of effort. For details, see Chapter 27.

(ii) **Myocardial infarction** : See Chapter 27.

(iii) **Cardiac arrhythmias** : Betablockers can

be used successfully in the treatment of tachyarrhythmias precipitated by sympathetic overactivity as during exercise, emotion and anaesthesia, and those occurring in patients with pheochromocytoma. They are also used as adjuncts in the treatment of atrial fibrillation and atrial flutter resistant to digitalis. For details, see Chapter 25.

(iv) **Hypertension** : Betablockers are valuable in the treatment of hypertension of all grades of severity. Betablockers should not be used alone in a patient suspected to have pheochromocytoma but may be used together with an alpha adrenergic blocking drug. For details, see Chapter 26.

(v) **Thyrotoxicosis** : Betablockers are valuable adjuncts to antithyroid drugs in the treatment of thyrotoxicosis, where they produce rapid symptomatic relief. They are invaluable in the treatment of thyrotoxic crisis. There is little justification for their use as the sole therapy for preparation of thyrotoxic patients for surgery. For details see Chapter 59.

(vi) **Hypertrophic obstructive cardiomyopathy** (Idiopathic hypertrophic subaortic stenosis) : This condition is characterised by a marked hypertrophy of the ventricular musculature, commonly of the left ventricle, leading to palpitation, angina, dyspnoea or syncope. Propranolol, in the dose of 60 to 400 mg. per day, causes a marked symptomatic improvement in majority of cases.

(vii) **Pheochromocytoma** : Alpha adrenergic blocking agents are routinely used prior to surgery in patients with pheochromocytoma to control the complication of hypertension during surgery. In some patients, however, alpha blockade leads to a severe tachycardia particularly when atropine is used for preanaesthetic medication. Propranolol, administered in the dose of 1-5 mg. intravenously, controls this complication. It should be pointed out, however, that beta blockade without simultaneous alpha blockade may lead to severe hyper-

tension in pheochromocytoma.

(viii) **Chronic open-angle glaucoma :** Although many beta-blockers have been tried, timolol maleate 0.25-0.5% is currently preferred. It is used locally as eye-drops and appears to be as effective as pilocarpine in lowering intraocular pressure. It has an advantage over pilocarpine in that it does not induce spasm of accommodation nor does it affect the pupil. Further, it is convenient to administer (once or twice daily). β -blockers can be used in conjunction with miotics and carbonic anhydrase inhibitors in resistant cases. In general, β -blockers used locally, seem to be well tolerated and reasonably safe even on long term use. However, patients should be carefully monitored for possible usual adverse reactions to the drug.

(ix) **Miscellaneous :** Increased adrenergic activity is prominent in anxiety states and propranolol can reduce the associated symptomatology such as palpitation, tachycardia, sweating and diarrhoea. Thus, the betablockers have been used to decrease cardiac symptoms prior to important meetings and public speaking engagements in susceptible individuals.

High plasma levels of catecholamines have been observed in decompensated cirrhosis. The non-selective beta blocker propranolol has been reported to reduce the frequency of G.I. bleeding

in patients with cirrhosis and esophageal varices.

Alpha and beta-adrenergic blocking drugs :

LABETALOL : This drug acts as a competitive antagonist at both alpha and beta-adrenergic receptor sites. Given orally, it reduces heart rate and myocardial contractility, slows A-V conduction, decreases peripheral resistance, and lowers blood pressure. It is a selective α_1 blocker while its action on beta is nonselective.

The drug undergoes extensive first pass metabolism. It is metabolized mainly by conjugation with glucuronic acid; less than 5% is excreted unchanged in urine.

Adverse reactions: Labetalol may cause G.I. disturbances, dryness of mouth and fluid retention. Cardiac effects include marked bradycardia, A-V conduction disturbances and rarely orthostatic hypotension. Other reactions include nervousness, sexual dysfunction, muscle cramps and depression. Patients on long term therapy may develop antinuclear antibodies but SLE is rare. The drug accumulates in tissues with high melanin content such as the choroid, and periodic eye examination is recommended.

Therapeutic uses : It is mainly used to treat high blood pressure and hypertensive emergencies. The treatment is started with 100 mg. twice daily and increased gradually to 400-800 mg. It can also be given i.v. slowly or by slow infusion in hypertensive emergencies.

15 Cholinergic Drugs

Parasympathomimetic or cholinergic agents are drugs which stimulate the effector cells innervated by postganglionic parasympathetic cholinergic nerves. In general, their actions are similar to those seen following the stimulation of the parasympathetic nervous system.

The parasympathomimetic agents may be classified as :

- I. Esters of choline e.g. acetylcholine, methacholine, carbachol and bethanechol.
- II. Cholinomimetic alkaloids e.g. pilocarpine, muscarine and arecholine.
- III. Cholinesterase inhibitors or anticholinesterases e.g. neostigmine, organophosphorus compounds.

ESTERS OF CHOLINE

Acetylcholine (ACh) is an ester of choline with acetic acid, while carbachol and bethanechol are esters of choline and betamethylcholine respectively with carbamic acid. The base choline also possesses properties similar to acetylcholine but the amount required to produce equivalent tissue response is large. Esterification of choline augments the activity markedly.

Chemically, acetylcholine and related substances are quaternary ammonium compounds and their unique specific action is attributed to the trimethylammonium $[R-N^+(CH_3)_3]$ groupings.

ACETYLCHOLINE : Acetylcholine is available in powder form as chloride or bromide; it is extremely hygroscopic. It rapidly undergoes hydrolysis in a neutral or alkaline medium and the

solution has to be preserved at an acidic pH. Given orally, it is rapidly destroyed in the gastrointestinal tract and hence, it has to be administered intravenously to elicit its pharmacological actions.

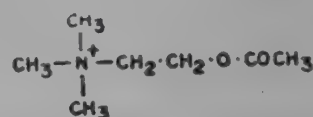


Fig. 15.1 : Acetylcholine.

Pharmacological actions : Acetylcholine, when given intravenously to intact animals, fails to produce several of its excitatory effects. Thus, even large doses of acetylcholine have no appreciable action on neuromuscular apparatus and only a feeble action at the autonomic ganglia and on smooth muscles. This is because a considerable amount of acetylcholine given intravenously is destroyed in the plasma by the enzyme pseudocholinesterase, and at the site of action by the specific true cholinesterase and is thus prevented from reaching a sufficient concentration at the effector cells. The only important action seen after intravenous injection of acetylcholine is a transient fall in blood pressure. Many of its actions, however, can be demonstrated in *in-vitro* preparations.

The pharmacological actions of acetylcholine can be divided into :

- (a) Muscarinic actions e.g. on gland cells, smooth muscles and the heart.
- (b) Nicotinic actions e.g. on autonomic ganglia, adrenal medulla and the motor end plates of skeletal muscles.

Muscarinic actions :

The actions produced as a result of acetylcholine released from the postganglionic parasympathetic nerve endings or the actions resulting from exogenously administered acetylcholine on the receptors of organs with postganglionic parasympathetic nerve supply are termed as '*muscarinic actions*'. The muscarinic actions of both endogenously released as well as exogenously administered acetylcholine are blocked by atropine. The designation 'muscarinic action' comes from the fact that these actions are similar to those produced by the poisonous mushroom alkaloid muscarine.

Recent evidence indicates the presence of subtypes of the muscarine receptors M1 and M2. Drug like pirenzepine, shows selectivity for receptors in specific tissues (G.I. tract). Muscarine receptors with M1 sensitivity are found in ganglia and the CNS whereas M2 sites exist at the post-ganglionic effector organs.

(1) Cardiovascular system :

(i) *Heart* : In mammals the effect of acetylcholine on the heart is similar to that obtained by stimulation of the vagus which is a cholinergic nerve. Thus, it depresses the sinoauricular node, slows down the heart and may produce cardiac arrest. It decreases the contractility and increases the conduction velocity of atria, while it tends to produce A-V block by depressing the A-V conduction. These changes are transient and can be blocked by atropine.

Acetylcholine reduces the cardiac rate in isolated heart preparation. However, in the presence of atropine, acetylcholine can stimulate the heart, causing ventricular arrhythmias.

(ii) *Blood vessels* : Acetylcholine tends to dilate the blood vessels mainly of the skin and the mucous membrane. It also dilates the coronary arteries and has a doubtful vasodilator effect on the cerebral and pulmonary blood vessels. ACh induced vasodilatation is a result of relaxation of the vascular smooth muscle. Intravenous ACh administration in man results in flushing, a sense of warmth in the skin and throbbing in the head.

The blood pressure falls as a result of a decrease in the total peripheral resistance and in the cardiac output (vagal effect) in anaesthetized animals.

(2) **Other smooth muscles:** Acetylcholine increases the tone and the rhythmic activity of the smooth muscle of the gastrointestinal tract and enhances peristalsis. The sphincters are, however, relaxed resulting in a rapid forward propulsion of the intestinal contents. Acetylcholine contracts the smooth muscle of the gall bladder and the urinary bladder while the smooth muscle of the trigonal sphincter is relaxed. The bronchial smooth muscle is constricted and this may contribute to development of apnoea. Bronchospasm produces a sense of substernal constriction in human beings. The smooth muscle of the ureter is usually contracted by ACh while the response of the uterus is inconsistent.

(3) **Secretions** : Cholinergic stimulation increases the gastric, intestinal and pancreatic secretions; the bronchial, salivary, lacrimal and nasopharyngeal secretions are also augmented. The increased bronchial secretions, accompanied by bronchospasm, may result in cough and dyspnoea. Acetylcholine also irritates the bronchial mucous membrane, predisposing to the development of cough. The salivary secretion induced by cholinergic stimulation is profuse and watery in character. As the postganglionic sympathetic fibres supplying the sweat glands are cholinergic, ACh enhances sweating.

(4) **Eye** : Instillation of acetylcholine in the eye is without any effect as it is not absorbed. However, injection of acetylcholine in the carotid artery after sectioning of the postganglionic fibres from superior cervical ganglion produces a constriction of the pupil (miosis) by contracting the circular fibres of sphincter pupillae. It also contracts the ciliary muscle which results in relaxation of the suspensory ligament (zonule) of the lens. This reduces the tension on the lens and allows the lens to bulge into the anterior chamber thereby increasing its thickness and reducing the focal length. Vision is, therefore, fixed for a short distance. This is termed *spasm of*

accommodation. By producing miosis, acetylcholine tends to reduce the intraocular tension by increasing the drainage of ocular fluid through the canal of Schlemm.

Nicotinic actions :

Administration of atropine blocks the muscarinic actions of acetylcholine; in such animal preparations, injection of large doses (1-5 mg) of acetylcholine still produces certain responses. These actions are due to an initial stimulation and subsequent blockade of the autonomic ganglia and the myoneural junction and are known as '*nicotinic actions*' as they resemble those produced by the tobacco alkaloid nicotine. The stimulant action of ACh on the autonomic ganglia is blocked by the ganglion blocking agents like hexamethonium while the action at the skeletal myoneural junction is antagonized by the alkaloid d-tubocurarine.

(1) Actions at the autonomic ganglia: Acetylcholine induced ganglionic stimulation results in an increased output of acetylcholine and noradrenaline from the postganglionic parasympathetic and sympathetic nerve endings respec-

tively. The effects of released noradrenaline can be demonstrated by using an atropinized preparation. In such a preparation the blood pressure shows a rise due to peripheral vasoconstriction. In addition, large doses of ACh also stimulate the adrenal medulla to increase the secretion of adrenaline which further augments and sustains the rise in blood pressure (Fig. 15.2).

(2) Action at the myoneural junction : Acetylcholine released as a result of stimulation of the somatic nerves or administered in sufficiently large doses initially induces contraction of the skeletal muscle. A very large concentration of ACh at the myoneural junction can produce paralysis of the skeletal muscles by keeping the muscle in a persistently depolarized state in which it is refractory to further stimuli. Intra-arterial injection of acetylcholine in the brachial artery of human volunteers produces fasciculations and twitching of the skeletal muscle followed by a prolonged weakness.

Miscellaneous actions : The recurrent collaterals of the motor neurones which synapse with the Renshaw cells of the spinal cord have

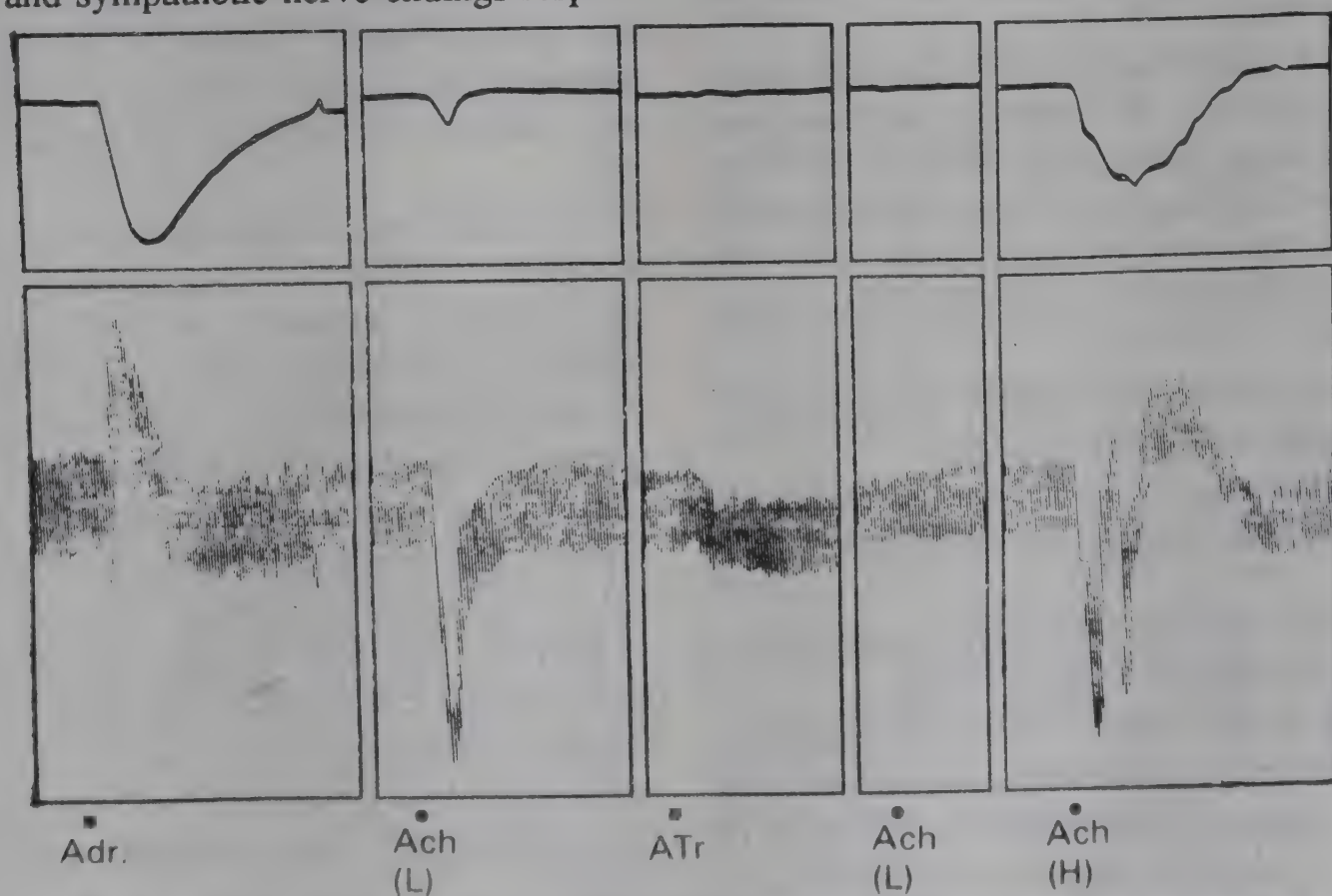


Fig. 15.2 : Blood pressure and spleen volume (upper tracing) in anaesthetised dog. Note the fall of B.P. following a low dose of acetylcholine (Ach) which is blocked by atropine (Muscarinic action). High dose of Ach in this atropinised animal produced rise in B.P. and contraction of the spleen (Nicotinic action), resembling the action of adrenaline (Adr.).

been demonstrated to be cholinergic and the receptors are predominantly nicotinic in nature. Both choline acetyl transferase and cholinesterase have been demonstrated in various areas of the central nervous system. Acetylcholine is a neurohumoral transmitter at certain sites in the CNS.

In contrast to the Renshaw cells, most of the cholinergic neurones at the cortical and subcortical levels of the CNS have predominately muscarinic receptors.

Considerable experimental evidence is now available indicating cholinergic involvement in behavioral responses. Clinically, patients with Huntington's disease, characterized by involuntary choreiform movements and dementia, have been found to have severe degeneration of cholinergic neurons within the basal ganglia. Patients suffering from Alzheimer's dementia have significant losses of an enzyme activity (choline acetyltransferase) in the basal ganglia, frontal cortex and hippocampus. It appears that a cholinergic system is essential to normal behaviour, but it is not sufficient to support any behaviour on its own.

Being a quaternary ammonium compound, ACh administered intravenously does not cross the blood brain barrier and hence it exerts no significant central actions. There is no single drug which can block all the actions of ACh. This means there are different types of ACh receptors such as:

- (1) Those blocked by atropine and responsible for mediating muscarinic actions.
- (2) Those blocked by tetraethylammonium and responsible for mediating ganglionic actions and
- (3) Those blocked by d-tubocurarine and responsible for skeletal muscular action.

Acetylcholine assay: Acetylcholine present in biological fluids is usually bioassayed by its ability to contract eserinizied dorsal muscle of leech or the rectus abdominis muscle of frog.

Therapeutic uses: Owing to its extremely transient action, ACh cannot be employed for any

therapeutic purpose. Hence, several acetylcholine substitutes have been synthesised to find out a drug that (i) will be effective orally as well as parenterally, (ii) will have more selective actions of sufficiently long duration.

METHACHOLINE : Methacholine differs from acetylcholine in being effective orally though its absorption on oral administration is variable. Susceptibility of methacholine to true cholinesterase is approximately 1/3rd that of acetylcholine. It is totally resistant to pseudocholinesterase and consequently possesses a longer duration of action. The drug is now rarely used in clinical practice.

CARBACHOL: Carbachol is more potent than methacholine and bethanechol. Carbachol is resistant to both true and pseudocholinesterase and is better absorbed from the gastrointestinal tract than other choline esters.

Pharmacological actions: Unlike ACh, carbachol has a relatively selective muscarinic effect on the smooth muscle of the gastrointestinal tract and the urinary bladder; it also stimulates autonomic ganglia and skeletal muscles and has a more sustained miotic effect on topical application.

Carbachol, when administered parenterally in therapeutic doses in man, produces flushing of the face, sweating, salivation and lacrimation. The increased gastrointestinal and urinary tract activity may produce desire for defaecation and micturition. Carbachol occasionally produces hypotension and syncope particularly in elderly subjects. *The muscarinic effects of carbachol are not adequately antagonized by atropine.*

Preparations and dosage: Carbachol tablet I.P. contains 1 mg. of the drug. Dose: 1 to 4 mg. Carbachol injection I.P. contains 0.25 mg. of carbachol in 1 ml. Dose : 0.25 to 0.5 mg by subcutaneous injection. For ophthalmic use, 3% eye drops.

BETHANECHOL (Urecholine) : Like car-

bachol, this choline ester, is resistant to hydrolysis by both true and pseudocholinesterase and has mainly muscarinic actions.

Like carbachol, it exerts effects mainly on the gastrointestinal tract and the urinary bladder. It has negligible cardiovascular effects. It has no significant nicotinic actions and unlike carbachol its muscarinic effects are well antagonized by atropine.

Preparations and dosage: Bethanechol is available as 5 or 10 mg. tablets. Dose: 10 to 30 mg. 3-4 times daily.

Adverse reactions to choline esters: These arise mostly as an extension of the pharmacological actions. Besides the minor side effects like G.I. disturbances, flushing, salivation, sweating and bradycardia, the serious adverse effects include hypotension, syncope, bronchial spasm, and occasionally cardiac arrhythmias or cardiac arrest.

Carbachol, because of its slow hydrolysis, is capable of exerting cumulative toxicity. Abdominal cramps, belching, nausea and vomiting may result. Hypotension, cardiac arrhythmias and death after parenteral carbachol therapy have been noted. Instillation of carbachol into the eye may produce ocular pain, impaired day vision and spasm of accommodation.

Carbachol and bethanechol should never be administered by intravenous route.

Therapeutic uses of choline esters :

(a) **Gastrointestinal and urinary tract:** Carbachol and bethanechol have often been employed for the treatment of post-operative paralytic ileus and abdominal distension following surgery and toxic states, for relief of gastric atony following bilateral vagotomy for peptic ulcer and in cases of urinary retention. Bethanechol by virtue of its wider margin of safety, is preferred to carbachol for this purpose. It is imperative to exclude the presence of organic obstruction, particularly in old people, before using these drugs. Bethanechol is administered in the dose of 15 to 30 mg. 3 to 4 times a day for paralytic ileus while for gastric atony, it is administered

along with meals (as it increases the gastric secretion) in the dose of 10 to 20 mg. The drug is also useful in selected cases of congenital megacolon. For acute urinary retention, a dose of 5 mg is adequate. It can be repeated after 10 to 15 minutes if necessary. In chronic urinary retention 10 mg. of the drug may be administered 3 to 4 times a day till voluntary or automatic voiding is established.

(b) **Glaucoma:** One drop of 0.75 - 3% solution of carbachol is instilled in the eye every 10 minutes to reduce the intra-ocular tension in wide angle glaucoma. However, pilocarpine is preferred for this purpose.

Contraindication for the use of choline esters:

(1) *Hyperthyroidism:* as these agents may precipitate cardiac arrhythmias.

(2) *Bronchial asthma:* because of the danger of aggravating or precipitating this condition.

(3) *Peptic ulcer :* as these agents increase the gastric secretion.

(4) *Myocardial infarction :* because of the danger of hypotension and development of conduction blocks.

CHOLINOMIMETIC ALKALOIDS

PILOCARPINE: Pilocarpine is an alkaloid obtained from the South American shrubs *Pilocarpus microphyllus* and *Pilocarpus jaborandi*. It acts by direct stimulation of the effector organs getting cholinergic innervation and produces both muscarinic and nicotinic actions of acetylcholine. The former are antagonized by atropine. Pilocarpine usually produces hypertension and tachycardia by stimulation of the sympathetic ganglia, particularly in spinal animals.

When applied topically to the eye, pilocarpine produces miosis, a transient increase followed by a more sustained fall in the intraocular tension and a spasm of accommodation.

Pilocarpine produces an initial stimulation of the central nervous system followed by depression.

Adverse reactions : It has all the side effects of choline esters. Because of the promi-

nent secretory response, pulmonary edema is a major hazard of systemic pilocarpine therapy.

Preparations and dosage: Pilocarpine nitrate eye drops N.F. contain 10 mg. of the drug per ml. Pilocarpine eye ointment N.F. is available in the same concentration.

Therapeutic uses : The drug is too toxic for systemic use.

Pilocarpine alone (0.5–4% aqueous solution) or in combination with 1 per cent eserine is used to reduce intraocular tension in acute congestive glaucoma. Pilocarpine induced miosis persists for 3 to 24 hours but the spasm of accommodation disappears in about 2 hours. Pilocarpine is often used alternately with mydriatics like homatropine (2 to 5 per cent) to break adhesions between iris and the lens.

Pilocarpine ocusert is a drug delivery unit specially designed to deliver pilocarpine slowly, over a period of 7 days. However, it is far more expensive than drops.

MUSCARINE AND ARECHOLINE : Muscarine is an alkaloid from the poisonous mushroom *Amanita muscaria*. Acute mushroom poisoning is characterised by diarrhoea, dyspnoea, abdominal pain, lacrimation, salivation, weakness, confusion, convulsions and coma. These effects are due to muscarine and can be antagonized by large doses of atropine. Delayed poisoning which develops within 6 to 15 hours after ingestion of another mushroom *Amanita phalloides* is characterised by nausea, vomiting, diarrhoea, jaundice and vasomotor collapse; this is attributed to other toxins and does not respond specifically to atropine. Muscarine has no therapeutic application. Arecholine, the alkaloid of betel nut *Areca catechu*, has cholinergic actions and was used as an anthelmintic in veterinary practice. It has no human therapeutic application.

CHOLINESTERASE INHIBITORS

Anticholinesterase (anti ChE) drugs act by inhibiting the enzymes true and pseudo-

cholinesterase, thus producing an accumulation of acetylcholine at the various cholinergic sites. The pharmacological effects of the anticholinesterases, thus resemble those of stimulation of the central, ganglionic and the peripheral cholinergic components of the nervous system. In addition, some of the anticholinesterases have independent pharmacological actions of their own. These agents can be classified as :

I. **Reversible :** Those that produce reversible inhibition of cholinesterase; e.g. physostigmine and neostigmine.

II. **Irreversible :** Those that induce practically irreversible inhibition of cholinesterase e.g. Di-isopropylfluorophosphate (DFP), Octa methyl pyrophosphotetramide (OMPA) and echothiophate.

Mechanism of action : Acetylcholine is postulated to be inactivated by combination with two sites on the enzyme cholinesterase: (i) an *anionic site* bearing a negative charge which attracts the quaternary nitrogen atom (N^+) of acetylcholine and (ii) an *esteratic site* which attracts the carboxyl group (COO) of the acetylcholine molecule. Similar sites have also been envisaged for the acetylcholine receptors on the organs having cholinergic innervation. As a result of the union of ACh with cholinesterase, the esteratic site of the enzyme is acetylated and this results in splitting off of choline. The acetyl group in combination with the esteratic site is, however, immediately removed as a result of combination with water, forming acetic acid. This sets the esteratic site of the enzyme free for further inactivation of acetylcholine.

The reversible anticholinesterases bear a structural resemblance to ACh. They are, therefore, capable of combining with the anionic and esteratic sites of cholinesterase as well as with ACh receptor. However, the complex which they form with the esteratic site of cholinesterase is much less readily hydrolyzed than the acetyl-esteratic site complex formed with acetylcholine. This produces a temporary inhibition of the enzyme. In contrast to other reversible anticholinesterases, edrophonium forms reversible

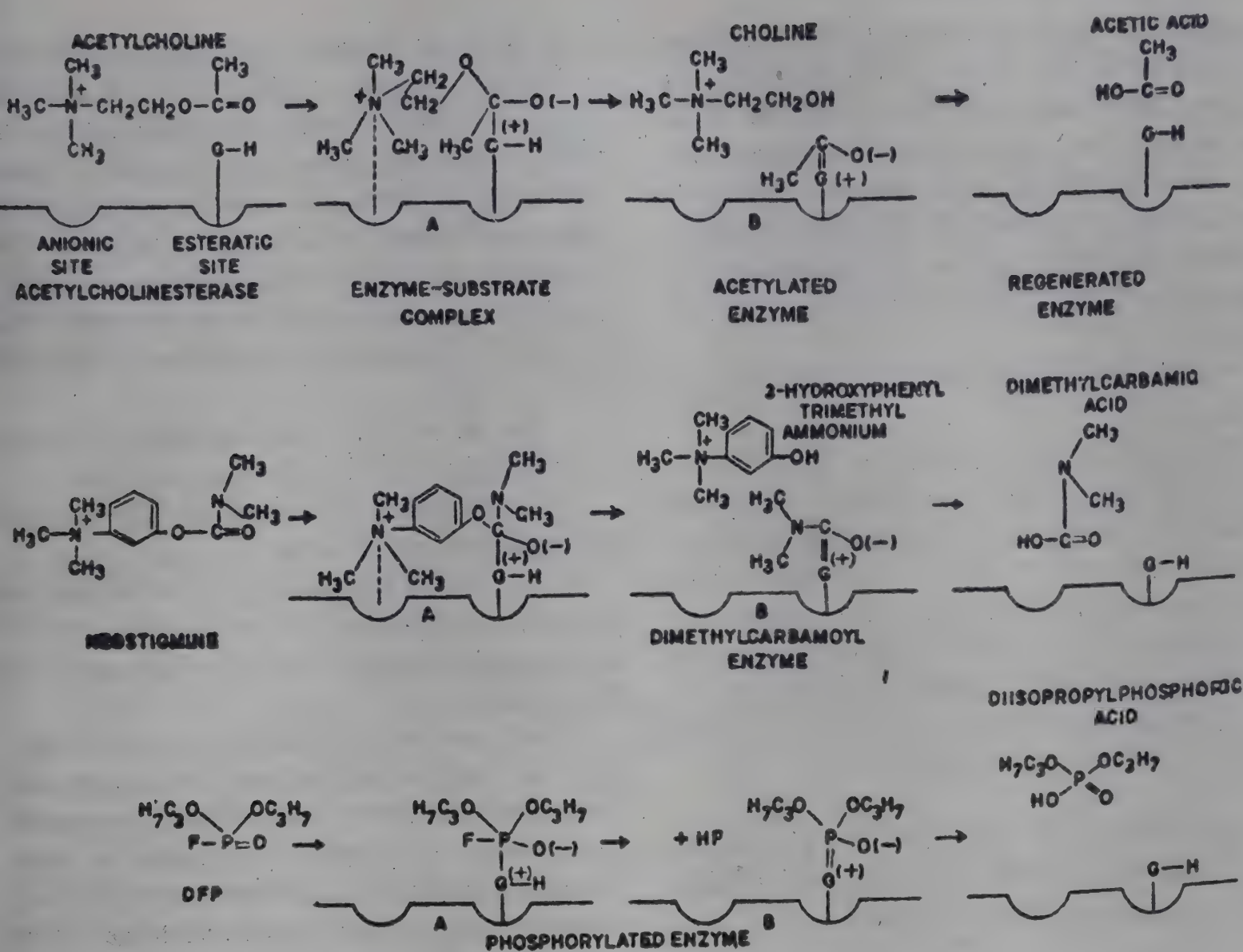


Fig. 15.3 : The inactivation of acetylcholine by cholinesterase and the mechanism of action of reversible anticholinesterase drug, Neostigmine, and irreversible anticholinesterase drug D.F.P.
G-H : a protonated acidic group of the esteratic site

complex only with the anionic site and hence, has a shorter duration of action.

The irreversible anticholinesterases, organophosphorus compounds, combine only with esteratic site of cholinesterase and consequently the esteratic site is phosphorylated. The hydrolysis of the phosphorylated site, however, is extremely slow and in certain cases does not occur at all. This produces an almost irreversible inhibition of cholinesterase. In contrast to other organophosphorus compounds, echothiophate forms complexes with both anionic and esteratic sites and hence, is much more potent than other organophosphorus compounds.

I. Reversible anticholinesterases:

The reversible anticholinesterases can be further divided into :

(a) Naturally occurring e.g. physostigmine.

(b) Synthetic : Neostigmine, Pyridostigmine, Ambenonium, Demecarium and Edrophonium.

PHYSOSTIGMINE (Eserine): Physostigmine is an alkaloid obtained from the calabar bean, the dried ripe seed of an African woody climber *Physostigma venenosum*.

Pharmacological actions : The majority of the pharmacological effects of physostigmine can be attributed to inhibition of true and pseudo-cholinesterase and are similar to those of other parasympathomimetic agents.

Topical instillation of the drug into the eye produces miosis, spasm of accommodation and a fall in intraocular tension. The drug is rapidly absorbed on oral or parenteral administration and crosses the blood brain barrier.

Preparations and dosage: Physostigmine

salicylate I.P. is used in eye as 0.1 to 1% aqueous solution or in the form of an oculentum. On storing, the solution becomes pink due to the formation of decomposition products which irritate the eye. The solution, therefore, should be prepared in acidic medium (pH 4 to 5) with the addition of a reducing agent like sodium metabisulphite and should be preserved in sealed containers.

Physostigmine salicylate inj. contains 2 mg./2 ml. ampoule.

Therapeutic Uses: Apart from its use in eye, physostigmine is considered relatively safe in the treatment of anticholinergic drug (atropine) intoxication, and of poisoning with phenothiazines and tricyclic antidepressants. It is particularly valuable in patients with C.N.S. symptoms such as delirium. It is used in doses of 2 mg. s.c. or i.v. and repeated after 10-20 min. If effective 2-4 mg. may be given every 2-4 hours.

NEOSTIGMINE: Neostigmine is a synthetic, quaternary ammonium compound that inhibits both true and pseudocholinesterases.

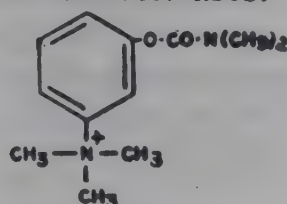


Fig. 15.4 : Neostigmine

Pharmacological actions : In addition to its anticholinesterase activity, neostigmine also directly stimulates certain organs receiving cholinergic innervation. The important actions are :

(a) **Gastrointestinal tract :** Neostigmine increases the tone and motility of the gut, enhances the production of gastric juice and by augmenting the motor activity of the small and large intestine, promotes the propulsion of intestinal contents. Atropine reduces but does not completely abolish the intestinal effects of neostigmine.

The effects of neostigmine on gastric secretion and motility and other areas of the gut are considerably reduced after bilateral vagotomy.

(b) **Skeletal muscles :** Neostigmine produces a striking increase in the power of skeletal muscles in patients with myasthenia gravis. In contrast to physostigmine, neostigmine, on intra-arterial administration, can stimulate chronically denervated muscle or a muscle in which all the cholinesterase has been inactivated by prior intra-arterial administration of an irreversible anti-ChE like D.F.P. Neostigmine is postulated to improve muscle power :

1. by its anti-ChE activity causing greater accumulation of ACh at the motor end plates.

2. by increasing the amount of ACh released during each nerve impulse and

3. by directly stimulating the cholinergic receptor sites on the motor end plate by virtue of its structural similarity with ACh. It thus acts as a partial agonist.

Administration of neostigmine to normal subjects is usually associated with twitchings and fasciculations of skeletal muscles but these are not encountered in myasthenic patients on neostigmine therapy. Neostigmine reverses the neuromuscular blockade produced by d-tubocurarine and gallamine, but is not a satisfactory antagonist for benzoquinonium and actually enhances the paralysis of skeletal muscles by persistent depolarizers like succinylcholine and decamethonium.

(c) **Cardiovascular system :** The drug usually reduces the heart rate and tends to lower blood pressure by peripheral vasodilatation and bradycardia. This effect is antagonized by the stimulation of the sympathetic ganglia. The ultimate outcome of pharmacological effects on the cardiovascular system is thus dependent upon an interplay of many complex factors and, therefore, unpredictable.

(d) **Eye :** Local instillation of the drug into the eye produces miosis, spasm of accommodation and reduction in intraocular tension. The drug, however, has poor penetrability as compared to physostigmine.

(e) **Autonomic ganglia :** In low concentrations, neostigmine stimulates the autonomic ganglia, while in large doses, it blocks them.

The drug does not cross the blood brain barrier in sufficient amounts and hence exerts less significant effects on the central nervous system.

(f) **Miscellaneous** : Like other cholinergic drugs it increases various secretions.

Neostigmine produces bronchoconstriction and increased ureteral peristalsis.

Absorption, fate and excretion : Neostigmine, being a quaternary ammonium compound, is not absorbed satisfactorily on oral administration. It is therefore, usually administered by subcutaneous or intramuscular injection. The effect of a single intramuscular injection becomes manifest within 10 minutes and persists for 3 to 4 hours. It is partly destroyed by the cholinesterase and partly eliminated in urine.

Preparations and dosage : Neostigmine bromide tablet I.P. contains 15 mg. of the drug. Dose : 15 to 30 mg. Neostigmine methyl-sulphate is available in ampoules containing 0.5 mg. per 1 ml. Dose : 0.5 to 2 mg.

PYRIDOSTIGMINE (Mestinon) : This compound, which structurally resembles neostigmine, shares its pharmacological actions. The drug, however, has a slightly longer duration of action. It is claimed to be better tolerated by myasthenic patients. The compound is less potent than neostigmine.

Preparations and dosage : Pyridostigmine bromide table B.P. contains 60 mg. of the drug. Dose : 60 to 240 mg. Pyridostigmine slow release tablets have a duration of action of 4 to 10 hours with a single dose. Pyridostigmine injection contains 1 mg. of the drug per ml. Dose : 1 to 5 mg. subcutaneously or intramuscularly.

AMBENONIUM (Mytelase) : Ambenonium is a bisymmetrical synthetic quaternary ammonium compound which is a more potent true cholinesterase inhibitor than neostigmine and has a more marked direct stimulant effect on the skeletal muscle. The action of the drug appears to be more sustained than that of neostigmine and it is claimed to have a lower incidence of gastrointestinal side effects.

It is available as 10 mg. tablets. dose: 5-20 mg 3-4 times a day as required.

DEMECARIUM (Humorsol) : Structurally, demecarium is made up of two neostigmine molecules joined through 10 methylene groups. The drug inhibits true cholinesterase more specifically than pseudocholinesterase more specifically than pseudocholinesterase. The drug is a powerful miotic on topical instillation. This effect reaches a peak within 4 hours and may last for 3 to 10 days. It is accompanied by a spasm of accommodation. It is used as 0.25 per cent solution in ophthalmic practice.

EDROPHONIUM (Tensilon) : Edrophonium, a quaternary ammonium anticholinesterase, is a white, crystalline powder, soluble in water. Structurally it is related to neostigmine. The drug has a weak anticholinesterase activity as compared to neostigmine but it enhances neuromuscular transmission with a dose that is too low to affect the smooth muscles, the myocardium and the glands. The latent period and duration of action of this compound are much shorter than in the case of neostigmine, the effects of a single intravenous therapeutic dose persisting only for 10 minutes. The muscarinic side effects are of smaller magnitude and countered effectively by atropine.

Preparations and dosage : Edrophonium chloride B.P. is available as 10 ml. vials containing 10 mg. of the drug per ml.

Adverse reactions to reversible anticholinesterases : The reversible anticholinesterases produce effects attributable mainly to their muscarinic actions. These are epigastric distress, salivation, sweating, lacrimation, paraesthesia, sense of constriction in chest, nausea, abdominal cramps, diarrhoea and fasciculations, particularly around the mouth and in the superior extremities. Hypotension and tremors have been occasionally reported.

Demecarium and eserine, on instillation into the eye may pass into the nose through the nasolacrimal duct and produce muscarinic side

effects. It is necessary to apply firm pressure on inner canthus of the eye during instillation to prevent passage of these agents into the nose. Demecarium may rarely increase intraocular tension in narrow angle glaucoma and may rarely cause retinal detachment.

When used in the treatment of myasthenia gravis, an overdose of these compounds may produce skeletal muscle paralysis by persistent depolarization. This phenomenon, termed cholinergic crisis, has to be differentiated from the sudden exacerbation of muscular weakness in myasthenia often associated with severe upper respiratory infection, termed myasthenic crisis. In myasthenic crisis, the requirement of the anti ChE agent is increased and occasionally the patient becomes resistant to anticholinesterase medication. Edrophonium administered intravenously in the dose of 2 mg. brings about a prompt improvement of muscle power in myasthenic crisis, while it exacerbates the weakness of cholinergic crisis. However, this effect is not dangerous because of the extremely short duration of action of edrophonium and its relative freedom from muscarinic side actions. If the initial dose of 2 mg. does not produce an improvement in muscle power within 30 seconds, a dose of 8 mg. may be administered further. The cholinergic crisis is treated by administration of large doses of atropine, oximes and artificial respiration.

Therapeutic uses of reversible anticholinesterases :

(a) **In the eye :** The reversible anti-cholinesterases are invaluable for reducing the increased intraocular tension in glaucoma. Glaucoma is a disease complex where intraocular pressure is increased and, if untreated, can cause irreversible damage. In acute congestive (narrow angle) glaucoma, the iris probably blocks the entrance to trabecular space at canal of Schlemm. This blockade by iris results in a precipitous increase in intraocular tension producing severe pain, nausea and often loss of vision due to optic atrophy. The contraction of sphincter of iris in-

duced by the anticholinesterases removes the iris blockade and facilitates the drainage of the intraocular fluid. The mechanism of reduction of tension in chronic wide (open) angle glaucoma by these agents is not definitely understood as there is no physical obstruction in this condition.

Acute congestive glaucoma is a medical emergency and a combination of pilocarpine nitrate (4%) with physostigmine salicylate (1%) is preferred. Adjuvants such as acetazolamide (a carbonic anhydrase inhibitor) are also employed (see Chapter 35). Once the attack is controlled a definitive surgery is advised.

Chronic (wide angle) simple glaucoma has insidious onset and needs almost permanent drug therapy. The drugs used are pilocarpine nitrate (0.5-4%), physostigmine salicylate, demecarium, β -blockers and sympathomimetic drugs such as 10% phenylephrine. Sufficient transconjunctival absorption of anti-ChE drugs can occur following their repeated instillation to cause systemic effects. Absorption can be minimised by digital compression of the inner canthus of the eye during and after instillation. Prolonged use of miotics may hasten cataract formation and may cause retinal detachment.

Physostigmine is employed 0.2 to 1 per cent 2 to 4 times daily. The short duration of action of physostigmine necessitates its repeated administration. Demecarium 0.1 to 0.25 per cent once or twice weekly overcomes this difficulty. For use of β -blocker timolol in glaucoma see Chapter 14.

Reversible anticholinesterases give fairly satisfactory results in glaucoma following cataract surgery. They have also been employed alternately with mydriatics to break adhesions between the iris and the lens or cornea.

(b) **Myasthenia gravis :** Myasthenia gravis is a disease characterised by easy fatigability and progressive weakness of striated muscles and with intermittent periods of exacerbation. Pregnancy usually leads to an improvement or even temporary remission of this condition.

Myasthenia gravis is now considered an autoimmune disease caused by a deficiency of the

postsynaptic neuromuscular acetylcholine receptor complex. Thus the receptors in myasthenic muscle are degraded and cleared much faster than normally. The number of available acetylcholine receptors in the involved muscles is reduced by as much as 70-90%. Circulating antibodies to acetylcholine receptors have been demonstrated in 70-90% of patients with myasthenia; this is of diagnostic value.

The diagnosis of myasthenia gravis depends upon typical clinical picture and a dramatic clinical response to either neostigmine or to edrophonium. Administration of 1 to 1.5 mg. of neostigmine intramuscularly produces a marked improvement in muscle power of myasthenic individuals, which lasts for a period of 3 to 4 hours. Atropine sulfate 0.6 mg. is usually administered intramuscularly before or along with neostigmine to counter the muscarinic side effects of the latter. Edrophonium can also be used for similar purpose.

Treatment of myasthenia gravis : Neostigmine was formerly the drug of choice in the treatment of myasthenia. however, because of its relatively short duration of action (3 to 4 hours and in some cases 1 hours), development of tolerance and waxing and waning of muscle strength, agents with a longer duration of action and fewer side effects, e.g. pyridostigmine and ambenonium are now preferred. These drugs may, however, be combined with neostigmine as the onset of action of neostigmine is quicker. The effect of parenteral neostigmine appears within 30 minutes while oral administration produces a response within 1 hour. The therapy is initiated with neostigmine (Prostigmine) 15 mg. orally, at a time, and the dose is gradually increased until the maximal benefit is obtained.

The reversible anticholinesterases are usually administered at intervals of 3 to 4 hours orally or parenterally to ensure a smooth and sustained effect. Parenteral medication is indicated before meals so as to enable the patient to swallow his food. Most myasthenics can be improved only to a certain level with these drugs. Thus, 80 to 90 per

cent recovery occurs only in 25 per cent individuals. Further increase in dosage precipitates toxic actions without appreciable increase in clinical improvement. It is, therefore, deemed wiser to accept minor disability rather than overdose the patient and risk adverse effects which may become incapacitating. Infection increases the requirements of anticholinesterases in myasthenia.

Ephedrine sulfate (25-50 mg. t.i.d.) and potassium chloride (1-2 g. t.i.d.) are often used as adjuvants to anti-ChE therapy in myasthenia.

Because of the probably autoimmune basis of myasthenia, prednisolone has been used in its management in the dose of 25-100 mg. once a day. It has been shown to benefit some patients who cannot be controlled adequately with anticholinesterases, as well as older patients with moderate to severe disease. such therapy may, however, cause exacerbation of weakness in the early stages and, therefore, needs supervision.

Several drugs like aminoglycoside antibiotics (streptomycin and kanamycin), phenytoin, phenothiazines and d-tubocurarine can aggravate muscle weakness and even produce myasthenic crisis in some patients with myasthenia gravis. They are better avoided in this condition.

(c) Treatment of curare poisoning : Edrophonium is preferred to neostigmine to antagonize curare induced skeletal muscle paralysis because of its short latent period of action. A single dose of 10 mg. may at times be inadequate and 2 or 3 doses may have to be administered.

(d) Gastrointestinal and urinary tract : Neostigmine is employed parenterally in the dose of 0.5 to 1 mg. in the treatment of postoperative paralytic ileus and urinary retention. The drug may be repeated, if necessary, at intervals of 4 to 6 hours. In paralytic ileus and distension, it is used as an adjuvant to other treatment. Neostigmine is used in the treatment of achalasia and in patients with marked dilatation of the oesophagus, because of its stimulant action on the lower end of the oesophagus. The drug, however, cannot induce peristalsis in the atonic small intestines in patients with advanced sprue.

Benzpyrinium is also employed for the treatment of post-operative paralytic ileus and urinary retention.

(e) **Cardiovascular system** : Neostigmine is preferred to choline esters in the treatment of paroxysmal atrial and supraventricular tachycardias as it is comparatively safer. It is usually injected subcutaneously in the dose of 0.5 to 2 mg.

Combination of choline esters and neostigmine is not advocated in cardiac arrhythmias as the drugs may occasionally produce alarming muscarinic effects resulting in death.

(f) **Snake venom poisoning** : Anticholinergics may be beneficial in the management of neurotoxic effects of Asian cobra venom toxicity. For this purpose, atropine sulfate (0.6 mg.) is given intravenously, slowly, and this is followed immediately by edrophonium chloride (Tensilon) 10 mg. intravenously over two minutes. Edrophonium not only reverses oculomotor and glossopharyngeal paralysis after cobra bite but also counters respiratory paralysis.

The pathophysiologic nature of paralysis after cobra bite is very similar to that of myasthenia gravis. Paralysis following krait bite is not likely to benefit from edrophonium therapy as the Krait beta - bungarotoxin causes pre-synaptic blockage.

Following intravenous edrophonium, the improvement can be maintained by a longer acting anticholinesterase such as neostigmine methylsulfate which can be given by continuous intravenous or subcutaneous infusion.

The dose of edrophonium for children is 0.25 mg/kg; that of atropine is 50 µg/kg.

II. Irreversible anticholinesterases :

The organic esters of phosphoric acid or the organophosphorus compounds are powerful inhibitors of cholinesterase. Unlike the quaternary ammonium Anti-ChE, most of these compounds have a high lipid solubility and can be absorbed from practically all the routes including the gastrointestinal tract, the intact unbroken skin, mu-

cous membranes and lungs. Because of their high lipid solubility, these compounds cross the blood brain barrier and affect the functions of the central nervous system.

The pharmacological effects of the organophosphorus compounds are those of acetylcholine which accumulates in the tissues on account of the prolonged inhibition of the true and pseudocholinesterases. The pseudocholinesterase is inhibited more readily than the true cholinesterase.

The organophosphorus compounds are inactivated in the body almost entirely by oxidation and hydrolysis and the end products are eliminated in urine.

The organophosphorus compounds include therapeutically useful agents like diisopropyl fluorophosphate (DFP), tetraethylpyrophosphate (TEPP) and echothiophate; insecticides like fenitrothion (Dalf) malathion (diazinon), mipafox, octamethylpyrophosphotetramide (OMPA), sumithion (Tik-20), and the highly toxic nerve gases, tabun, sarin and soman synthesized for chemical warfare.

Therapeutic uses : The organophosphorus compounds have limited therapeutic uses owing to their prolonged action and high toxicity.

(i) **In the eye** : DFP solution 0.1 per cent in peanut oil was initially employed for reducing intraocular tension in glaucoma. The oily menstrum of the drug, however, produced sensitivity reactions precluding the use of this drug. The compound currently favoured for topical use is echothiophate in the concentration of 0.06 per cent. The reduction in the intraocular tension with this drug persists for 1 to 3 weeks following a single instillation. The compound however, produces a marked ciliary spasm, browache, headache and blurring of vision. The major drawback of long acting anti-ChE agents is the risk of development of lenticular opacities following their prolonged use (6 months or more).

(ii) Dichloroovas and trichlorophone have anthelmintic properties. See Chapter 55.

ORGANOPHOSPHORUS COMPOUND POISONING

Poisoning with organophosphorus compounds may be (1) occupational as in persons engaged in spraying insecticides, (2) accidental e.g. by consumption of the agricultural products sprayed with these insecticides or (3) suicidal due to intentional ingestion of any of these compounds.

Symptomatology : The effects of acute intoxication are mainly manifested as muscarinic and nicotinic signs and symptoms.

(a) *Muscarinic effects* : Localized exposure of the eyes produces miosis, spasm of accommodation, headache and conjunctival hyperaemia. Inhalation results in bronchospasm, cough and augmented bronchiolar secretions and a sense of 'tightness in the chest'. On ingestion, the gastrointestinal symptoms are the earliest to appear and consist of anorexia, nausea, vomiting, abdominal cramps, tenesmus and diarrhoea. The other muscarinic effects, including those on the eye and the respiratory system, appear subsequently. Of these, severe bronchospasm and pulmonary edema may be fatal.

(b) *Nicotinic effects* : These are characterised by fasciculations, twitching, generalized weakness and a depolarization type of paralysis. There may be either tachycardia or bradycardia.

(c) *Central effects* : These include giddiness, anxiety, confusion, ataxia, hypotension, respiratory depression, convulsions and coma. Death is usually due to respiratory failure.

The duration of effect is longest with DFP and shorter with echothiophate and TEPP.

(d) *Miscellaneous effects* : In addition to the acute toxic manifestations mentioned above, DFP and mipafox may produce demyelination of the nerve tracts in the central and peripheral nervous systems e.g. the spinocerebellar tract, pyramidal tract and the sciatic nerve, producing permanent functional derangements. This produces weakness, fatiguability, twitching and loss of tendon reflexes, ultimately leading to paralysis. Adulteration of edible olive oil with lubricating oil

containing triorthocresyl phosphate (TOCP) caused thousands of deaths in a tragedy that occurred in North Africa. Unfortunately, no treatment is available for the neurotoxic syndrome.

Treatment of acute poisoning : As recommended by the WHO Expert Committee (Technical Report 513), "The treatment must be instituted rapidly in order to prevent a fatal outcome. In intoxication by mouth, rapid gastric lavage is imperative. For removal of secretions and maintenance of a patent airway, place the patient in a prone position with head down and to one side, the mandible elevated and the tongue pulled forward. Clear the mouth and pharynx with finger or suction. Use an oropharyngeal or nasopharyngeal airway or endotracheal intubation if airway obstruction persists. If the body is soiled with the insecticides or if vomiting or hypersalivation has occurred, clothes must be removed and the skin washed with soap and water for at least 10 minutes. Contamination of the eyes is treated by washing of the conjunctiva".

"On signs of systemic absorption, both atropine and reactivators (see below) must be given parenterally. Persons without signs of respiratory insufficiency but with manifest peripheral symptoms should be treated with 2-4 mg. of atropine sulfate and 1-2 g. of a soluble salt of pralidoxime (P-2-AM) or 250 mg. of obidoxime chloride (adult doses) by slow intravenous injection. More atropine (with or without the reactivator) may be given depending upon the severity of the intoxication and the response to the first dose. After the administration of oximes, less atropine may be required.

Severely intoxicated, unconscious persons with respiratory difficulties and convulsions should be given atropine and a reactivator as above. In addition to this, the airway must be kept free and artificial ventilation applied if required. *Mouth to mouth respiration is to be avoided* when it is suspected that the patient has been intoxicated by mouth since vomited material may contain dangerous amounts of toxic substances. *Atropine should not be given to a cyanotic patient until the*

cyanosis has been overcome, since this may lead to ventricular fibrillation.

In these cases of severe intoxication, 4-6 mg. of atropine sulfate should be given initially, followed by repeated doses of 2 mg. or as much as required to maintain full atropinization. The patient's condition, including respiration, convulsions, blood pressure, pulse frequency, and salivation should be carefully observed as a guide to further administration of atropine. Initially, atropine may have to be given at 5 or 10 minute intervals. Cases are described in the literature in which several hundred mg. have been given during the first 24 hours. Usually however, it is not necessary to exceed 50 mg. Every 2 mg. dose gives a short-lasting improvement of respiration and reduction in cyanosis and convulsions. Tachycardia may occur and watch must be kept on salivary secretion in order to prevent over-atropinization. The pulse rate should not be allowed to exceed 120/min. There may also be a short-lasting improvement in miosis.

If possible, blood samples should be taken for cholinesterase determinations before and during the treatment. In parathion poisoning, reactivation of the enzyme activity of the red blood cells may be observed within one hour, but if the patient comes late to the treatment (after 36 hours) oxime therapy may be less effective.

Because most intoxications occur after exposure of the skin or after ingestion, *any deterioration in the patient's condition due to delayed absorption into the circulation must be carefully watched for.* Reactivators are excreted fairly rapidly if kidney function is normal (in the case of pralidoxime 80 per cent in 2-3 hours) and repeated doses of 1 g. may be needed.

The intravenous injection of oximes should be made slowly, especially in small children."

Atropine is effective in antagonizing the central and peripheral muscarinic effects but does not modify the ganglionic action and the neuromuscular paralysis.

The additional supportive measures include:

- (i) Treatment of shock.
- (ii) Administration of antibiotics to prevent secondary infection.
- (iii) Continued vigilance, as a relapse may occur as late as a week after apparent recovery.

OXIMES (Cholinesterase reactivators): The irreversible inhibition of cholinesterase produced by the organophosphorus compounds is due to phosphorylation of the esteratic site of the enzyme. Oximes are drugs which combine with the phosphoryl groups of these phosphorylated esteratic sites forming a soluble complex. This results in setting free the esteratic site and a reactivation of the enzyme.

The oximes are particularly effective in reversing the neuromuscular paralysis due to organophosphorus compounds where atropine is ineffective. Their effects on the autonomic ganglia and the central nervous system are not significant, except probably in the case of D.A.M. and M.I.N.A. which cross the blood brain barrier. These compounds are effective only when administered within a short time after poisoning. Late administration fails to produce the expected results. They are mainly metabolized in the liver and the breakdown products are eliminated in urine.

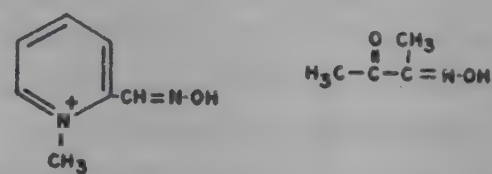


Fig. 15.5 : P-2-AM

DAM

The oximes available for therapy are :

- (i) Pyridine-2-aldoxime choride (P-2-AM, Pralidoxime) injected i.v. slowly in the dose of 1-2 g. The dose can be repeated after 1-2 hours. It can also be given intramuscularly, 1 gm in 3 ml of water. It is also available as 1 g tablets for use in milder cases.

- (ii) Diacetylmonoxime (D.A.M.) administered in the dose of 1-2 g. intravenously slowly

(200 mg/minute). It crosses the blood brain barrier and can reactivate AChE in the CNS. The dose can be repeated after 20 minutes.

(iii) Obidoxime chloride is more potent than pralidoxime. It is given intravenously in the dose of 3-6 mg/kg. The dose can be repeated every 20 minutes.

The oximes are not free from toxicity. They

may produce local irritation, drowsiness, giddiness, blurred vision, diplopia, tachycardia and hypotension. Pralidoxime has weak anti-ChE activity and hence contraindicated in the treatment of overdose with neostigmine or physostigmine. High doses of pralidoxime and related compounds can themselves cause neuromuscular blockade.

16 Cholinergic Blocking Drugs

The parasympathetic or cholinergic blocking agents include atropine, and related alkaloids obtained from the plants *Atropa belladonna* (the deadly nightshade), *Atropa acuminata*, *Hyoscyamus niger* (henbane), *Scopola carniolica* and *Datura stramonium* (Datura) and synthetic or semisynthetic atropine substitutes. These drugs in therapeutic doses predominantly block the muscarinic actions of acetylcholine; the ganglionic and skeletal neuromuscular actions of acetylcholine are not affected.

BELLADONNA ALKALOIDS

The name *Atropa belladonna* represents a paradox. For whereas Atropos is the seniormost of the Three Fates who performs the unglorious function of cutting the thread of life, the term belladonna (pretty lady) is derived from the practice by Venetian court beauties of putting the extract of these plants in the eyes, to impart them a 'lustre'. Belladonna preparations were known to ancient Hindus for many centuries.

The two important alkaloids of Belladonna are atropine (dl-hyoscyamine) and hyoscine (scopolamine). Atropine is an ester of an aromatic organic acid 'tropic acid' with a complex organic base 'tropine' while hyoscine is an ester of tropic acid with another base 'scopine'. There is only a minor difference in the structures of scopine and tropine. Belladonna preparations and atropine are the most commonly used anticholinergic drugs.

Mechanism of action : The belladonna alkaloids block the muscarinic effects of endogenous as well as externally administered ACh, by competing with acetylcholine for the muscarinic receptors. They do not interfere with the re-

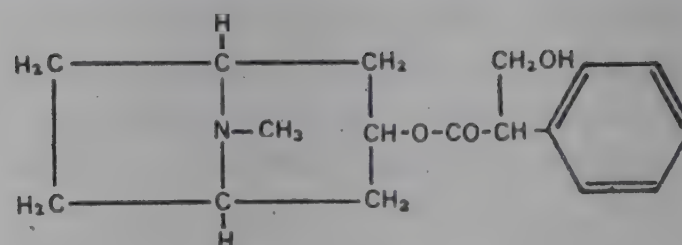


Fig 16.1a : Atropine

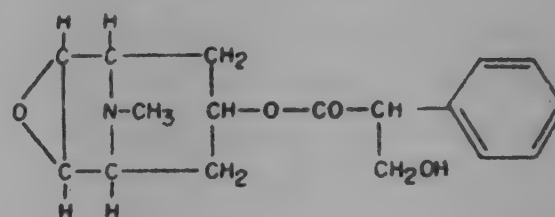


Fig. 16.1b: Scopolamine

lease of ACh at the cholinergic nerve endings. Atropine can be visualised as having the same affinity for the muscarinic receptors as acetylcholine but because of its poor intrinsic activity, atropine-receptor combination does not elicit a prominent muscarinic response. The antagonism between acetylcholine and atropine is of *competitive type* which is reversed by an increase in the concentration of acetylcholine at the muscarinic neuroeffector site.

Atropine is more effective in blocking the effects of externally administered acetylcholine than the effects of cholinergic nerve stimulation. Again, the dose of the drug required to produce muscarinic blockade varies from organ to organ. Thus, salivary secretion is extremely sensitive to atropine blockade, while the smooth muscle of the gastrointestinal tract, the eye and the heart are less affected even when relatively large doses are administered systemically. In the CNS, cholinergic transmission at subcortical and cortical levels is predominantly muscarinic and can be blocked by atropine.

Although atropine can completely abolish the

effects of choline esters on the gastrointestinal tract, it does not completely abolish the effects of vagal stimulation.

Although atropine is a specific inhibitor of the muscarinic effects, it can in very large doses block the nicotinic action of acetylcholine at the autonomic ganglia and the myoneural junction. It can also block the actions of histamine, 5-hydroxytryptamine and adrenaline. However, such concentrations as are required for this purpose are never achieved in the body with therapeutic doses and hence, these actions have little practical significance. The blockade of autonomic ganglia is marked on parenteral administration of atropine substitutes containing the quaternary ammonium (NH_4) ion.

Pharmacological actions : The pharmacological actions of atropine and scopolamine (hyoscine) are qualitatively similar except that atropine is a central nervous system stimulant while scopolamine is a central depressant and can act as a sedative. Scopolamine has more prominent effects on the iris, the ciliary body and the salivary, bronchial and sweat secretions while atropine is more active on the heart, the gut and the bronchial smooth muscle. Atropine has a longer duration of action than scopolamine.

Secretions : The belladonna alkaloids reduce the secretions of the exocrine glands except the production of milk.

(a) *Salivary secretion* : Atropine can block the copious watery salivary secretion induced by parasympathetic stimulation. The vasodilatation in the salivary glands which accompanies salivation following stimulation of chorda tympani in animals is claimed to be due to synthesis of a local vasodilator polypeptide and is not affected by atropine.

(b) *Gastric secretion* : Atropine can reduce the volume and the total acidity of gastric secretion. The secretion of acid without any food in the stomach (interdigestive secretion) is significantly diminished and may even be completely abolished by full doses of atropine. The psychic, gastric and intestinal phases of gastric secretion are, however, only reduced partially. Atropine

reduces the gastric secretion produced by caffeine, histamine and alcohol also partially. Atropine reduces the secretion of mucin and enzymes in the gastric juice and also blocks the gastric secretion elicited by the parasympathomimetic agents.

(c) *Other secretions* :

Atropine has little effect on the secretion of pancreatic and intestinal juices or bile. It reduces the secretions in the nose, mouth, pharynx and bronchi. The bronchial secretions may become viscid after atropine. It inhibits the sweat secretion even in small doses but does not produce a striking inhibition of the lacrimal secretion.

Smooth muscle :

(a) *Gastrointestinal tract* : Atropine reduces both the tone and the motility of all parts of the gastrointestinal tract. Atropine antagonizes the spasmogenic action of morphine on small and large intestines and can also completely abolish the excessive motility induced by the parasympathomimetic agents. It is, however, only partially effective in blocking the effects of vagus nerve stimulation and it does not interfere significantly with normal peristalsis.

(b) *Biliary tract* : Atropine exerts a weak antispasmodic action on the biliary tract and the gallbladder. Its action on the biliary sphincter is unpredictable.

(c) *Urinary tract* : Atropine has been demonstrated to produce reduction in normal as well as in drug induced ureteral peristalsis. It does not completely abolish the bladder response to stimulation of the sacral parasympathetic fibres. Therapeutic doses tend to reduce the tone of the fundus of the bladder and enhance the tone of the trigonal sphincter and may cause urinary retention.

(d) *Bronchi* : Atropine relaxes the smooth muscles of the bronchi and bronchioles. It is particularly effective in relieving bronchoconstriction produced by parasympathomimetic agents but is much less potent than adrenaline in relieving histamine induced bronchoconstriction. Since it dries up the secretions, it is not recommended in the treatment of bronchial asthma.

(e) *Uterus* : Atropine has no significant effect on the tone and motility of the uterine smooth muscle. Scopolamine, when administered during labour for its central sedative effect, does not interfere with uterine activity.

Eye : On local instillation, atropine produces mydriasis by blocking the cholinergic nerves supplying the smooth muscle of the sphincter of the iris. The ciliary smooth muscle is likewise paralysed by atropine. This produces a tightening of the suspensory ligament resulting in flattening of the lens with a consequent increase in its focal length. The individual, therefore, is able to see things clearly only at a long distance owing to fixing of lens for far vision. Because of sphincter paralysis, he cannot constrict the pupils for viewing near objects clearly or in response to bright light and therefore suffers from photophobia. This phenomenon is termed as *paralysis of accommodation or cycloplegia*. Atropine is thus both a mydriatic and a cycloplegic drug. Unlike scopolamine, conventional doses of atropine administered systemically do not produce significant ocular effects. Local instillation of 1 per cent atropine drops produces maximum mydriatic response within 30 to 40 minutes and recovery occurs within 7 to 10 days. Maximum cycloplegia with atropine is seen within 1 to 3 days; it persists for 7 to 11 days.

Atropine mydriasis can be distinguished from the mydriatic effect of sympathomimetic amines as the latter do not produce cycloplegia. Atropine does not alter the intraocular tension in the normal eye but in individuals with shallow anterior chambers and in those with *narrow angle glaucoma*, a precipitous increase in intraocular tension may occur after instillation of atropine or its substitutes. This effect is due to relaxation of the ciliary muscle and crowding of the iris in the angle of the anterior chamber of the eye interfering with the drainage of aqueous humour.

Cardiovascular system : Atropine, in therapeutic doses, may initially decrease the heart rate owing to its action as a partial agonist of acetylcholine or owing to stimulation of the

medullary vagal nuclei. This effect is usually followed by tachycardia, particularly in young individuals who have a high vagal tone and in whom the heart rate may increase by 30 to 40 beats per minute. Cardiac arrhythmias are rare. Accelerator action of atropine is sometimes not observed in old people and in infants even with large doses, probably because of the low vagal tone. Atropine abolishes the effects of parasympathomimetic agents on the heart rate and also the bradycardia induced by manoeuvres like carotid massage and pressure on an eyeball.

In therapeutic doses, atropine completely counters the peripheral vasodilatation and hypotension produced by parasympathomimetic agents. However, by itself it has insignificant effect on the vasculature and does not modify the blood pressure. Toxic doses of atropine produce dilatation of the cutaneous blood vessels resulting in 'atropine flush' and hypotension as a result of either depression of the vasomotor centre or peripheral vasomotor paralysis.

Central nervous system : Atropine, in therapeutic doses, has no effect on the central nervous system except a mild stimulation of the medullary vagal nuclei. This occasionally produces bradycardia and an increase in the rate and depth of respiration. Respiratory depression produced by toxic doses of anticholinesterases can be antagonized appreciably by atropine administration. Atropine in moderate doses controls the tremors and rigidity in parkinsonism.

In contrast to atropine, therapeutic doses of scopolamine administered subcutaneously, usually produce euphoria, drowsiness, amnesia and dreamless sleep with a reduction in REM sleep. The sleep lasts for 1 to 2 hours.

E.E.G. desynchronization (low voltage, fast activity) produced by reversible and irreversible anticholinesterases is abolished by both atropine and scopolamine. Both atropine and scopolamine depress the reticular activating system and antagonize the arousal response evoked by direct electrical stimulation, photostimulation or drugs; the E.E.G. tends to achieve synchronization (high

voltage, slow activity) and is similar to that seen in barbiturate sleep. Scopolamine is approximately 100 times more potent than atropine in depressing the reticular activating system.

Although toxic doses of atropine produce marked excitation in man or animals, the E.E.G. shows synchronization characteristic of sleep. The explanation of this paradox is not known.

Scopolamine owes its salutary effect in motion sickness probably to its action on the vestibular function.

Absorption, fate and excretion : The belladonna alkaloids are satisfactorily absorbed from the gastrointestinal tract, from parenteral sites of administration and from mucous membranes. The absorption from the eye and intact unbroken skin, however, is not significant. Atropine is partly detoxified in liver and partly excreted unchanged by kidneys. Approximately 50 per cent of the parenterally administered drug appears in the urine in free form within 24 hours while 33 per cent is excreted as unknown metabolites. Scopolamine is mostly metabolized.

Atropine crosses the placental barrier and is secreted in milk and saliva. Some rabbits possess the enzyme atropine-esterase in the plasma and the liver and are able to detoxify atropine much more rapidly than human beings. Such rabbits and certain other animals like rats and mice detoxify atropine faster than human beings and hence can tolerate large doses without toxicity.

Adverse reactions : Majority of these are in fact due to extension of its pharmacological actions and include dryness of mouth, difficulty in swallowing, fever, constipation, blurring of vision and retention of urine in elderly. Atropine can precipitate glaucoma in elderly persons. Locally, atropine can give rise to allergic reactions such as dermatitis, conjunctivitis and swelling of eye lids. Other toxic manifestations include :

(a) **Intolerance :** Intolerance to atropine in the form of local dermatitis and skin rash has been reported. Scopolamine may occasionally produce edema of the uvula glottis and lips.

(b) **Acute belladonna poisoning:** Atropine has a wide margin of safety. The lethal dose

of atropine is not known but is believed to be 10-20 mg. in children and 80-130 mg. in adults, although doses over 200 mg. in adults have been survived. Scopolamine is claimed to be more toxic than atropine. Fatal atropine poisoning is commoner in children, when it is administered systemically in the treatment of nocturnal enuresis. Application of belladonna plaster over large denuded surfaces may produce systemic absorption leading to intoxication. Poisoning may also occur following ingestion of leaves or seeds of *Datura* species.

The symptoms and signs are mainly due to peripheral muscarinic blockade and the central actions. Dryness of mouth, difficulty in swallowing, intense thirst, tachycardia, palpitation, flushing, hyperpyrexia due to inhibition of sweating, dilatation of pupils, blurred vision and photophobia are the cardinal manifestations of peripheral muscarinic blockade. Urinary urgency, difficulty in micturition and even retention of urine may appear as a result of spasm of the trigone. A rash may appear especially over the face, neck and upper part of the trunk, leading to desquamation of the skin.

The central effects are attributed to initial stimulation and subsequent depression of the central nervous system. The patient shows excitement, restlessness, motor incoordination, slurring of speech, disturbance of memory, confusion, hallucinations, and occasionally mania and delirium. Nausea, vomiting and hypertension are infrequent. Severe poisoning depresses the vasomotor centre, produces capillary dilatation leading to vasomotor collapse, coma and paralysis of the respiratory centre. Depression following initial excitement tends to appear more quickly with scopolamine.

Belladonna poisoning may be diagnosed by adding a drop of patient's urine into a cat's eye, where it will produce pupillary dilatation. However, absence of such dilatation does not exclude belladonna poisoning. Dry mucous membranes, dilated nonreacting pupils, flushing, rash, fever and rapid feeble pulse seen in atropine poisoning may sometimes be mistaken for an exanthema-

tous fever.

Treatment : If the poison has been ingested, prompt attempts to remove the poison by gastric lavage should be made. Alkaloidal inactivators like universal antidote should be administered before and after gastric lavage. Potassium permanganate, however, does not destroy atropine. The muscarinic effects can be countered by administration of parasympathomimetic agents like slow intravenous physostigmine 1-4 mg. (0.5-1 mg. in children) or neostigmine 2 to 5 mg. subcutaneously. The drugs may be repeated at intervals of 1-2 hours till satisfactory control over muscarinic blockade is established. Physostigmine is preferred in patients with C.N.S. symptoms. Restlessness and delirium may be treated with paraldehyde and diazepam but these compounds may augment the respiratory depression seen in later stages of atropine intoxication and should be administered cautiously.

A dark room to alleviate photophobia, catheterization for urinary retention, tepid sponging and ice bags for pyrexia, good nursing care, oxygen and artificial ventilation in the event of severe respiratory depression, constitute the supportive treatment.

(c) **Chronic atropine poisoning** is manifested by dryness of mouth, skin eruptions, tremors and speech disturbances.

Preparations and dosage :

(i) Belladonna dry extract I.P. contains 1 per cent of the alkaloids of Belladonna herb.

(ii) Belladonna tincture contains 0.03 per cent w/v of the alkaloids of belladonna herb, calculated as hyoscyamine in 70 per cent alcohol. It is clear green or brownish green liquid. Dose : 0.6 to 2 ml. by mouth.

(iii) Atropine sulfate I.P. may be administered orally as 0.5 mg. tablets or in powder form. Dose : 0.25 to 2 mg.

(iv) Atropine eye ointment I.P. contains 1 per cent atropine sulfate.

(v) Atropine sulfate injection I.P. contains 0.5 mg. of atropine sulfate in 1 ml. Dose 0.25 mg. to 2 mg. by subcutaneous or intramuscular injection.

(vi) Atropine methonitrate is used as a 0.6%

alcoholic solution in the dose of 0.2-0.6 mg.

(vii) Hyoscyamus tincture I.P. contains 0.05 per cent of hyoscyamus alkaloids. It has a greenish brown colour. Dose : 2 to 4 ml. by mouth.

(viii) Hyoscine (Scopolamine) injection I.P. contains 0.4 mg. of hyoscine hydrobromide in 1 ml. Dose : 0.3 to 0.6 mg. by subcutaneous injection.

(ix) Hyoscine hydrobromide tablets 0.3-0.6 mg. Dose 1-2 tablets 4 times daily.

Therapeutic uses of belladonna alkaloids :

(a) **As antispasmodic :**

(i) *Gastrointestinal colic* : The belladonna alkaloids are used to control hypermotility and pain associated with diarrhoea and dysenteries. Diarrhoea as a result of therapy with guanethidine and reserpine usually responds to belladonna alkaloids. Constipation due to spastic state of the bowel may be relieved after atropine. It also controls spasticity induced by lead and morphine.

Atropine in large doses is occasionally administered parenterally to facilitate roentgenological differentiation between a morphological defect and a functional spasm of the gastrointestinal smooth muscle.

Although occasional beneficial reports with the use of these compounds in pylorospasm, cardiospasm or hypertrophic pyloric stenosis are available, their routine use is not recommended. In fact, atropine may convert a partial organic pyloric stenosis to functionally complete obstruction.

(ii) *Other smooth muscle colics* : Although atropine has only a weak relaxant effect on the smooth muscle of the biliary tract, it is usually administered along with morphine in the treatment of biliary colic. Morphine tends to increase the intra-biliary pressure and this effect is countered by concomitant atropine administration. Atropine morphine combination is also used for relief of renal colic.

Atropine is often used to allay the frequency and urgency of micturition accompanying cystitis. It acts probably by increasing the capacity of the bladder as a result of its relaxant effect on the

bladder wall. Frequency of micturition associated with paraplegia is also controlled with atropine and it may be employed to control nocturnal enuresis in children.

(iii) *In peptic ulcer* : The belladonna alkaloids at best can only serve as adjuvants to dietary therapy and antacids in the treatment of peptic ulcer. They reduce smooth muscle spasm and the secretion of hydrochloric acid. However, the dose which is required to achieve a significant reduction in gastric acidity invariably produces adverse effects. (See Chapter 39).

(b) *In eye* : Atropine is used to produce mydriasis and cycloplegia. Mydriasis is necessary for a thorough fundoscopic examination and in the treatment of acute iritis, iridocyclitis and keratitis. Atropine reduces pain in these conditions probably by relaxing the inflamed musculature of iris and the ciliary body. Atropine may be instilled into the eye alternately with miotics to break the adhesions between the iris and the lens or the cornea. When maximum cycloplegia is desired e.g. in correction of accommodative esotropia, atropine is preferred. Otherwise, short acting atropine substitutes may be employed. Atropine is also useful in correcting accommodation spasm.

(c) *As pre-anaesthetic medication* : The details of this use are discussed in Chapter 5. Contrary to popular belief belladonna alkaloids do not abolish the laryngospasm during anaesthesia but prevent its development by reducing the respiratory secretions. These drugs are administered at least 30 minutes before general anaesthesia. Use of atropine with non-irritant, volatile general anaesthetics may produce unpleasant sore throat postoperatively. Similarly, reduction in the bronchial secretion can lead to inspissation of the residual secretions and formation of viscid bronchial plugs. The latter are difficult to remove and may produce atelectasis and secondary infection in debilitated individuals with chronic lung disease.

(d) *In organophosphorus poisoning* : This has been discussed in detail in Chapter 15. Atropine is also useful in mushroom poisoning due to mus-

carine.

(e) *In parkinsonism* : See Chapter 19.

(f) *In cardiovascular conditions* : Atropine may be useful in abolishing A-V block due to excessive vagal activity. It is also occasionally useful in countering the syncope and bradycardia due to hypersensitive carotid sinus.

(g) Both the natural belladonna alkaloids and various synthetic substitutes like dicylomine, propantheline have been used to treat urinary incontinence.

(h) *Hyoscine in motion sickness* : Hyoscine (scopolamine) hydrobromide in the dose of 0.5 to 1 mg. by mouth is used in the treatment of motion sickness. Dryness of mouth signifies the onset of effect and the protection conferred lasts for 4 to 6 hours. The greatest advantage of the drug is that, when given orally in above doses, it has only a slight sedative effect. Hyoscine is admirably suited to control motion sickness during journeys of short duration. In the event of prolongation of the journey, the drug may be repeated at the intervals of 2 hours in the dose of 0.1 mg. Larger doses may produce excessive sedation. Atropine is much less effective than hyoscine in controlling motion sickness. These drugs are of no value in preventing or abolishing nausea and vomiting due to other causes.

(i) *Hyoscine as sedative* : Hyoscine-morphine combination containing 0.4 mg. of hyoscine and 10 mg. of morphine has been used during labour to induce 'twilight sleep'. Hyoscine, in addition to its sedative effect, also produces amnesia. However, it may sometimes produce excitement and delirium.

Belladonna preparations for topical application e.g. belladonna plaster, liniment and ointment are not useful because even though atropine has a mild local anaesthetic effect, this action is therapeutically insignificant.

Precautions with atropine therapy : Atropine should be administered with caution in :

(a) Patients over the age of 40 as it may precipitate an attack of acute congestive glaucoma.

(b) Individuals with enlarged prostate, as

retention of urine may develop.

(c) Chronic lung conditions as it may produce drying and reduce the secretions.

(d) Congestive cardiac failure with tachycardia and

(e) Pyloric obstruction.

Atropine with neostigmine used for the treatment of d-tubocurarine toxicity may precipitate cardiac arrest.

SYNTHETIC AND SEMISYNTHETIC ATROPINE SUBSTITUTES

The need for atropine substitutes arises mainly because of the lack of selectivity in action of belladonna alkaloids. Thus, the dose of atropine required to produce the therapeutic effects on gastrointestinal tract, invariably produces numerous adverse effects. Drugs have been synthesized, therefore, to produce more therapeutic selectivity, when used locally or systemically. Unfortunately, there is no such ideal atropine substitute.

These substitutes are employed mainly for their predominant actions:

- I. as mydriatics and cycloplegics in the eye,
- II. as antispasmodics and
- III. in pharmacotherapy of parkinsonism.

Some of the substitutes find application at more than one site.

I. MAINLY USED IN EYE

In the eye, atropine substitutes are used:

- (i) for their shorter duration of action,
- (ii) for selectively more mydriatic or cycloplegic action, and
- (iii) in cases of atropine intolerance.

The drugs available are :

HOMATROPINE : Homatropine hydrobromide is used in the eye as 1-2 per cent solution. The onset of mydriasis and cycloplegia is similar to that with atropine but in contrast to atropine, the effects persist for 1-3 days. Homatropine is not

ideal for producing complete cycloplegia

EUCATROPINE HYDROCHLORIDE: This drug, instilled in the concentration of 2-5 per cent, produces mydriasis within 30 minutes lasting for 12 to 24 hours. Interference with accommodation is minimal. The drug is used in ophthalmoscopic examination of retina when mydriasis with less cycloplegia is required.

CYCLOPENTOLATE: Cyclopentolate, used in the concentration of 0.5 to 1 per cent, is a superior mydriatic and cycloplegic than homatropine. Mydriasis develops within 45 to 60 minutes while cycloplegia is established within 1 hour. The action last for 12-24 hours. Cyclopentolate can increase the intraocular tension and has been reported to produce restlessness, disturbed speech, disorientation, ataxia, amnesia, hallucinations and acute psychotic reactions in children.

The other drugs used for their action on the eye include Tropicamide (0.5-1%), Atropine methonitrate (0.5-1%) and Dibutoline (5-10%). The first is shorter acting than the other two. Dibutoline has also been tried parenterally in the treatment of spastic disorders of biliary, gastrointestinal and urinary tracts.

II. MAINLY USED AS SPASMOLYTICS

The spasmolytic atropine substitutes are mainly used in the treatment of peptic ulcer and colics. The quaternary ammonium atropine substitutes are relatively free from the central effects of belladonna alkaloids but are more liable to produce ganglionic blockade, resulting in impotence, postural hypotension, urinary retention and aggravation of pyloric stenosis. They may also block neuromuscular transmission by a curarimimetic action and produce respiratory paralysis. The duration of action, however, is longer than that of the belladonna alkaloids. There are many antimuscarinic drugs available for therapeutic use. The commonly used ones are:

ATROPINE METHONITRATE: Besides its ophthalmic use this compound is administered orally in the dose of 0.2 to 0.4 mg. 4 to 6 times a day in the treatment of congenital hypertrophic pyloric stenosis. The results, however, are variable.

METHSCOPOLAMINE BROMIDE : This quaternary ammonium compound is devoid of the central effects of scopolamine and is used in the treatment of peptic ulcer, renal colic and frequency of micturition associated with cystitis. Dose : 2 to 5 mg. orally, three times a day, or parenterally in the dose of 0.25 to 1 mg. Methscopolamine nitrate has similar application.

METHANTHELINE (Banthine): It is a synthetic quaternary ammonium compound with a high ratio of ganglion blocking to muscarinic blocking activity. The gastrointestinal effects of this drug are probably greater than those of atropine. The duration of action on oral administration is 6 hours as compared to 4 hours with atropine. The drug may produce impotence, postural hypotension, urinary retention and neuromuscular blockade. Other effects like euphoria, restlessness, acute psychosis and exfoliative dermatitis have been reported. The drug is administered in the dose of 50 to 100 mg. orally or 15 to 25 mg. by intramuscular injection.

PROPANTHELINE (Probanthine): It is related to methantheline and is claimed to possess more potent ganglionic and muscarinic blocking actions than methantheline. It is used in peptic ulcer, for relieving pain of diverticulitis and in the treatment of diarrhoea. It is administered orally in the dose of 30 to 45 mg. 6 hourly or intramuscu-

larly in the dose of 10 to 20 mg.

OXYPHENONIUM (Antrenyl) : This quaternary ammonium compound has a higher ratio of ganglion blocking to antimuscarinic activity than majority of other synthetic atropine substitutes. The usual dose is 10 mg. orally. It is available as 5 mg. tablets.

PIRENZEPINE : This is a tricyclic compound which acts on muscarine receptor to block selectively gastric secretion in such doses at which other antimuscarinic effects such as mydriasis, inhibition of gastric emptying and tachycardia do not occur. The drug has been used to treat duodenal ulcer (see Chapter 38).

Dicyclomine B.P., a tertiary amine, also has direct relaxant properties. Dicyclomine hydrochloride is available as 10 mg. tablets and as a syrup containing 10 mg. per 5 ml. Dose : 10-20 mg. 3 times a day. Use smaller doses in children.

Miscellaneous : Some of the other atropine substitutes available for therapy are homatropine methylbromide, hyoscine-N-butylbromide (Buscopan), diphemanil, pipenzolate (Piptal), poldine, clidinium, procyclidine, glycopyrronium and pavatrine. Many of these quaternary antimuscarinic drugs in tolerated doses are claimed to be superior to atropine. None, however, can be considered as highly selective in action, and clinically effective doses will evoke some adverse effects.

Belladonna substitutes used mainly in the treatment of parkinsonism are discussed in Chapter 19.

17 Ganglion Stimulating and Blocking Drugs

The ganglion stimulating agents have hardly any value in therapeutics. The important agents belonging to this group are the alkaloids nicotine and lobeline. In addition, synthetic compounds like tetramethylammonium (T.M.A.) and dimethylphenylpiperazinium (D.M.P.P.) are mainly used as experimental tools. Although nicotine has no therapeutic utility, it is the important constituent of tobacco. Lobeline has been discussed in Chapter 10.

NICOTINE : Nicotine was isolated from leaves of the tobacco plant, *Nicotiana tabacum* in 1828. The pharmacological actions of this compound, particularly its effects on autonomic ganglia, were studied by Langley and Dickinson in their classical experiments in 1889.

Pharmacological actions:

The amounts of nicotine absorbed during smoking are sufficient to produce measurable pharmacological and psychopharmacological effects.

(a) **Behavioral effects:** These vary according to the species and the dosage used. In small doses, the effects are predominantly stimulant, whereas large doses cause depression. In small doses it may improve attention, learning, reaction time and problem solving. Smokers often report pleasure and reduced anger, tension, depression and stress.

(b) **Central Nervous System:** Nicotine stimulates the central nervous system and produces tremors, while large doses may produce convulsions. These effects can be blocked by anticonvulsants, antiparkinsonian drugs and

hypnotics. Nicotine in small doses reflexly stimulates respiration through aortic and carotid body chemoreceptors; while large doses directly stimulate the medullary respiratory centre. The stimulation of respiration is usually followed by respiratory depression and paralysis.

Vomiting induced by nicotine is due to stimulation of the chemoreceptor trigger zone (C.T.Z.) and the sensory nerve endings involved in mediation of the vomiting reflex.

Nicotine, by stimulating the supraoptic nuclei of the hypothalamus, induces the release of A.D.H. and exerts an antidiuretic effect. In sensitive individuals, this effect may become apparent after smoking 2 or 3 cigarettes.

(c) **Autonomic ganglia :** Like acetylcholine, nicotine initially stimulates the autonomic ganglia by rapidly depolarising the cell bodies, leading to stimulation of post-ganglionic nerves. However, large doses of nicotine produce persistent depolarization of these cell bodies so that they cannot be further stimulated by preganglionic release of acetylcholine. This results in ganglionic blockade. Nicotine blockade does not interfere with the synaptic release of acetylcholine. In larger doses nicotine, by competing with acetylcholine for ganglionic receptor sites, also produces a competitive block. Nicotine in large doses, therefore, paralyses the autonomic ganglia by a dual mechanism.

The adrenal medulla, which is anatomically and embryologically a sympathetic ganglion, is initially stimulated by nicotine, leading to discharge of adrenaline into the blood stream. Larger doses block the secretory response to splanchnic nerve stimulation.

The ganglionic actions of nicotine are shared by T.M.A. and D.M.P.P. ; however, the ganglionic stimulation is not usually followed by paralysis.

The actions of nicotine in an intact animal usually vary according to preponderance of sympathetic or parasympathetic stimulation.

The most consistent effect of smoking in humans is an increase in the heart rate and peripheral vasoconstriction. Blood pressure may rise and an increase in skeletal muscle and coronary blood flow may occur. These effects result from increased release of catecholamine due to stimulation of the sympathetic ganglia and adrenal medulla.

Nicotine increases the motility and the tone of the gastrointestinal tract and occasionally produces diarrhoea. These effects are mainly due to stimulation of the parasympathetic ganglia. Stimulation is usually followed by decrease in motility and tone, leading to constipation. Nicotine initially increases the salivary and bronchial secretions, followed by their inhibition. Salivation accompanying smoking, however, is due to irritant nature of the smoke rather than its nicotine content.

(d) **Myoneural junction:** At the myoneural junction, nicotine produces a transient depolarization of the motor end plate, resulting in a stimulation of skeletal muscles and twitchings. In large doses, this stimulant effect is followed and often overshadowed by paralysis of myoneural transmission. The paralytic effect is akin to that seen with d-tubocurarine and is usually the cause of death in nicotine poisoning. It must be pointed out, however, that nicotine has a much more prominent effect on the autonomic ganglia than on the myoneural junction.

Both T.M.A. and D.M.P.P. have negligible effect on myoneural transmission.

(e) **Miscellaneous:** Intradermal injection or local application of nicotine produces sweating and vasoconstriction in the area treated. This effect is attributed to cutaneous axon reflexes mediated by sympathetic nerves and serves as a

basis for testing the integrity of the postganglionic sympathetic fibres. It is blocked by local anaesthetics, atropine and ganglionic blocking agents.

Tolerance: Nicotine tolerance is demonstrated by tobacco habituation. A chronic smoker is able to withstand large amounts of nicotine in contrast to a non-smoker. Inhalation of cigarette smoke enhances the metabolism of various drugs including nicotine in man because of induction of hepatic microsomal enzymes.

Absorption, fate and excretion : Nicotine is well absorbed from all mucous membranes and even from intact, unbroken skin. After absorption, it is concentrated in the liver, lungs and the brain. At physiologic pH, about 30% of nicotine is unionized and can cross readily cell membrane. A major portion of the alkaloid is metabolised and products are excreted by the kidney. An acidic urine enhances the excretion of free nicotine. Nicotine may be secreted in the milk.

Unlike nicotine, the quaternary ammonium ganglion stimulants T.M.A. and D.M.P.P. are not satisfactorily absorbed from the gastrointestinal tract. The compounds are not metabolised in the body and are excreted unchanged by the kidneys.

Adverse reactions: Acute nicotine poisoning occurs in workers engaged in spraying nicotine as an insecticide. Nicotine poisoning may occur in children from accidental ingestion of cigarettes. Evidence indicates that nicotine is much less toxic when swallowed in the form of tobacco than when ingested in pure form. It is, however, one of the most toxic agents and can produce death with the rapidity of cyanide. Acute nicotine poisoning is characterised by nausea, salivation, vomiting, abdominal pain and diarrhoea. Dizziness, headache, confusion and marked weakness develop. The pupils initially constrict but dilate subsequently. The initial rise in blood pressure is followed by a fall and initial bradycardia is followed by tachycardia. Cold sweat is a prominent feature. Respiration, after brief stimulation, becomes irregular. Convulsions may appear in the later stage and death occurs from respiratory paralysis.

The treatment consists of gastric lavage with

1:10,000 solution of potassium permanganate. As nicotine is rapidly metabolized in the body attempts should be made to tide over the crisis by symptomatic therapy. Paralysis of respiration should be treated by artificial ventilation with oxygen. Use of analeptics is dangerous.

Chronic nicotine poisoning and tobacco smoking : Tobacco, the dried leaf of *Nicotiana tabacum*, is used in various forms as snuff, as plug for chewing and for smoking. The nicotine content of tobacco varies from 0.5 to 8 per cent. Appreciable quantities of nicotine are absorbed from the inhaled smoke and a person who 'drags' on his cigar or cigarette absorbs larger quantities. In addition to nicotine, the other ingredients of tobacco smoke include pyridine, volatile acids, furfural and carbon monoxide.

Smoking and tobacco chewing are believed to be either causative or exacerbating factors in a number of conditions. Cigarette smoking has been shown to be associated with increase in morbidity and a shortening of life expectancy in general. The latter is related to the magnitude of cigarette consumption. It is higher in older than in younger persons, is seen especially in those who start smoking early in life and in those who inhale the smoke deeply. The increase in mortality is lower in those who give up smoking than in those who continue to smoke.

Most of the increase in mortality is from cancer of the lung, chronic bronchitis, emphysema and ischemic heart disease.

Carcinoma of the lung : The risk of carcinoma of the lung is 15-20 times higher in cigarette smokers than in non-smokers. This is especially so when cigarette smoking is combined with inhalation of asbestos dust, chromates, nickel, arsenic or radioactive material. Autopsy studies have shown extensive metaplastic changes in the bronchi in cigarette smokers. Tobacco smoke contains several cancer initiators (carcinogens) and cancer promoters (co-carcinogens); all have not been identified but the best known is benzapyrene. Experimental cancer of the skin has been produced in animals by application of conden-

sates of tobacco smoke and dogs who inhaled cigarette smoke through tracheostomies developed cancer of the lung.

Chronic bronchitis and emphysema: The incidence of chronic bronchitis is higher in habitual smokers than in non-smokers. A smoker's respiratory syndrome characterised by dyspnoea, wheezing, pain in chest and frequent infection of the upper respiratory tract has been described. Tobacco smoke contains a number of irritants which cause bronchoconstriction, damage to the ciliated epithelium and hypertrophy of the mucus glands. When younger smokers give up smoking their lung function returns to normal. However, when older persons with established chronic bronchitis and emphysema stop smoking, the benefit is less dramatic but still worthwhile.

Ischaemic heart disease : Mortality from ischaemic heart disease and the frequency of angina pectoris are more in smokers than in non-smokers. Further atherosclerotic changes are more extensive in smokers than in non-smokers. These effects are probably due to release of catecholamines from the adrenal medulla by nicotine. Catecholamines (a) increase platelet adhesiveness, (b) increase the concentration of blood lipids, and (c) increase the tendency to hypertension and cardiac arrhythmias. Further, smoking increases the concentration of carboxyhemoglobin in the blood. This has also been incriminated as an offender in the pathogenesis of ischaemic heart disease in smokers. Nicotine inhibits the release of PGI₂ from the blood vessels.

Peripheral vascular disease: T.A.O. occurs far more frequently in smokers than in non-smokers and intermittent claudication is more frequent in elderly atherosclerotic smokers than in non-smokers. Nicotine causes prolonged vasoconstriction in the hands and feet.

Tobacco amblyopia: Tobacco amblyopia which usually causes a gradual, but occasionally sudden, decrease in the visual acuity, particularly in the central field, is attributed to a spasm of the retinal blood vessels caused by nicotine. Fortunately, it is rare. Smoking may sometimes pro-

duce an abnormal increase in the intraocular tension in glaucomatous patients.

Miscellaneous : Women who smoke during pregnancy have been noted to have a higher incidence of abortions and to give birth to babies with below-average birth weights. In patients with peptic ulcer, smoking aggravates the pain, interferes with response to antacid therapy and retards the healing of ulcer. Increased incidence of cancers of the mouth, larynx, oesophagus and bladder has also been reported in association with smoking. Smoking is often claimed to have a tranquillizing effect but many people feel better both physically and mentally after giving up smoking.

Cigarette smoking accelerates the metabolism of drugs. The exact agent responsible for this is not known.

Treatment : Tobacco produces a psychological rather than a physical dependence. Abrupt cessation of heavy smoking may cause irritability and drowsiness. The treatment, therefore, consists of appealing to patients' reason. Psychotic and neurotic traits are found consistently more often in smokers than in non-smokers. Attention to any underlying psychological disturbances may prove very useful.

Prevention, however, is more important. In this respect, education of the children in the concept of positive health and in the harmful effect of smoking on health is of prime importance. This must be done as much by practice as by preaching since children tend to imitate the grown-ups around them and cannot be expected not to smoke as long as they see people particularly family members smoking all around them.

Doctors can help by inquiring about the smoking habits of all their patients, by educating them about its harmful effects and by strongly advising against smoking. In order to achieve a substantial success within the society, one obviously would need a sincere co-operation among the educationists, sociologists, cigarette manufacturers and the government alike.

Uses of ganglion stimulant : The ganglion stimulants are used as tools in experimental work.

GANGLION BLOCKING AGENTS: The ganglion blocking agents are drugs which block the transmission across the autonomic ganglia. The blockade produced by these agents, unlike that produced by nicotine, is not preceded by stimulation. These compounds are discussed in Chapter 26.

18 Skeletal Muscle Relaxants

Drugs acting as effective muscle relaxants are desirable in a wide variety of conditions. Thus, skeletal muscle relaxants able to reduce unwanted spasm or spasticity without interfering with consciousness and normal voluntary movements may find an important application in various neurological or musculo-skeletal disorders. Such drugs would also be valuable to surgeons during operative procedures, for achieving satisfactory muscle relaxation.

The exact mechanism by which normal skeletal muscle tone is regulated is not known, but it is probably dependent on the stretch reflex. The reticular formation of the brain stem is believed to exert augmentatory as well as inhibitory effects on the muscle tone through the internuncial neurons of the spinal cord.

Spasticity is due to increase in skeletal muscle tone associated with decrease in skeletal muscle power due to damage to the corticomotoneuronic pathways as in cerebral palsy, multiple sclerosis, C.N.S. injury or stroke. *Spasm*, on the other hand, is an involuntary contraction of muscle or group of muscles usually attended by pain and limited function.

Skeletal muscle relaxation without the loss of consciousness can be achieved by :

I. Drugs acting centrally e.g. diazepam and chlormezanone (See Chapter 11); baclofen, mephensin and similar compounds (See Table 18.1).

II. Drugs acting peripherally at neuromuscular junction producing either (a) competitive block e.g. d-tubocurarine or (b) depolarization block e.g. succinylcholine and decamethonium.

III. Drugs acting directly on muscle e.g. Dantrolene.

IV. Drugs effective in parkinsonism (See Chapter 19).

CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS

Centrally acting muscle relaxants cause muscular relaxation without loss of consciousness. Hence, they are expected to act on selective areas in the CNS. However, most of these drugs cause sedation; and sedative anxiolytic agents like diazepam also have central muscle relaxant action. The exact central mechanism of muscle relaxant action is not known, although these compounds depress spinal polysynaptic reflexes preferentially over monosynaptic reflexes. Some also have an action on the reticular neuronal mechanisms controlling the muscle tone.

DIAZEPAM: This drug has been discussed in detail in Chapter 11. It is useful alone, or in combination, for relieving spasticity especially in patients with lesions affecting the spinal cord, and occasionally in patients with cerebral palsy and multiple sclerosis. Painful spasms associated with pathological processes of the spinal cord are often reduced. It is not so useful in patients with cerebral lesions. It may be of benefit in the stiff-man syndrome and in localised muscle spasms due to various traumatic causes. It is the drug of choice to control spasms caused by tetanus toxin, where it can be given intramuscularly or intravenously. *Diazepam should not be mixed with other drugs for intravenous use.* It is given orally in the dose of 2 mg twice daily, and is increased gradually to maximum of 10 mg. 3-4 times daily.

Other centrally acting muscle relaxants are summarized in Table 18.1 For details, refer to the previous edition of this book. Experimentally, these compounds depress spinal polysynaptic reflexes preferentially over monosynaptic reflexes. They also act on the lateral reticular area of the brainstem. Most of these drugs produce some sedation. They are of some use in cases with localized muscle spasm but not so much in spasticity.

Table 18.1 Centrally acting muscle relaxants

Name	Preparation	Total daily dose
Benzodiazepines		
e.g. diazepam.	See Chap. 11	
Mephenesin carbamate (<i>Tolseram</i>)	Tab. 0.5 g	1—3 g.
Chlorphesin carbamate	Tab. 0.4 g	1.2—2.4 g.
Carisopradol (<i>Carisoma</i>)	Tab. 0.35 g.	0.7—1.4 g.
Chlorzoxazone (<i>Parafon</i>)	Tab. 0.25 g.	0.5—1.5 g.
Methocarbamol* (<i>Robaxin</i>)	Tab. 0.5 g.	4—8 g.
Orphenadrine*	Tab. 0.1 g.	0.1—0.2 g.

Oral doses mentioned are usually given in divided doses.

* I.M. and I.V. preparations available.

The centrally acting skeletal muscle relaxants should be used with caution in pregnant women and in the presence of renal damage. They are contraindicated in myasthenia gravis.

Various muscle relaxants described above have been advocated in such conditions as fibrositis, myalgia, myositis and spasms associated with arthritis. They are also recommended in certain spastic neurological disorders. However, there is no clear evidence that any of these agents influences neuronal conduction in man when given orally. Animal experiments have shown that these drugs reduce the activity of polysynaptic reflexes in the cord. But it must be emphasised that their ability to reduce decerebrate rigidity in cats does not necessarily indicate their usefulness

in the cerebrate man. The borderline beneficial effects observed with these agents are probably because of their central sedative and analgesic actions, and none of these compounds except diazepam, dantrolene, and baclofen can be recommended as effective, reliable and specific muscle relaxants.

BACLOFEN (Lioresal): This compound, beta-4 (chlorophenyl)-gamma aminobutyric acid, has been developed on the basis of the observation that gamma aminobutyric acid (GABA) acts as an inhibitory substance in the spinal cord. It is a powerful neuronal depressant, mainly acting in the spinal cord, on presynaptic mechanisms rather than on postsynaptic GABA receptors. It reduces the release of excitatory transmitters, and also causes a dose-dependent 'antinociceptive' effect in the intact animal; it may thus be useful in pain syndromes. Clinically, it produces considerable relief of painful flexor (and sometimes extensor) spasms and increased flexor tone in patients with complete or partial spinal transection. It also reduces tonic flexor dystonias of the lower extremities in patients with spinal spasticity. The drug may also improve bladder and bowel control in patients with spinal lesions. It is, however, not useful in other types of spasticity, such as that of cerebral origin. It has been also found to be a 'back up' drug in the treatment of trigeminal neuralgia.

It is used in the dose of 5 mg 3-4 times a day to be increased every 3-4 days, upto a maximum of 80 mg per day. It is almost completely absorbed, and 80% is excreted unchanged in the urine within 72 hours. The drug is generally well tolerated. The adverse effects include drowsiness, lassitude, hallucinations, depression, blurred vision and G.I. disturbances. It causes less muscle weakness than dantrolene.

DANTROLENE (Dantrium): This synthetic compound relaxes the skeletal muscle by a direct action on the contractile mechanism within the muscle. It is administered orally in the dose of 25

mg thrice daily, increasing gradually to a total of 300 mg per day. The benefits from this drug are not noticed for a week or longer. It does not alter the neuromuscular transmission. It reduces the depolarization-induced calcium release into sarcoplasm caused by conducted muscle action potentials. Thus, the muscle contraction is weakened by dantrolene although the electromyogram is unchanged. It has relatively little effect on cardiac and smooth muscle. The drug is particularly useful for the treatment of spasticity (especially cerebral spasticity) in patients in whom nursing care is made difficult by muscle contraction. Patients in whom spastic dystonic stiffness is useful as a sort of protective endogenous crutch should not be treated with dantrolene. Given orally, it is incompletely (about 1/3) absorbed and is largely metabolized in the liver. The adverse effects include generalised muscle weakness, dizziness, drowsiness, fatigue and diarrhoea. Rarely, it may cause serious hepatotoxicity.

Intravenous dantrolene is life saving in *malignant hyperpyrexia*, a rare, highly fatal and familial disorder, triggered by any potent inhalation anaesthetic, depolarising muscle relaxant, curare-like neuromuscular blocking agent and even by stress. In susceptible individuals, these can cause hyperpyrexia (temperature more than 42°C) and metabolic acidosis, a medical emergency.

It must be noted that management of the patient with spasticity implies more than just treatment of the spasticity. For many patients the increased tone of spasticity is not harmful and to some it may even be beneficial. Active measures to reduce spasticity are only justified where the reflex hyperexcitability positively interferes with function, making the rehabilitation programme, physiotherapy and nursing care difficult.

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

The contraction of the skeletal muscle in response to a nerve impulse can be blocked peripherally by:

(i) blocking the transmission of impulse across

the motor nerve e.g. local anaesthetics.

(ii) inhibiting the synthesis of acetylcholine in the motor nerve e.g. hemicholinium.

(iii) inhibiting the release of acetylcholine as with the toxin produced by the organism *Clostridium botulinum* and

(iv) modifying the motor end plate so that it does not respond to acetylcholine.

The first three approaches are not practicable for obvious reasons and paralysis of skeletal muscles is usually induced by interference with the function of motor end plate. The peripherally acting skeletal muscle relaxants owe their effect to this mode of action.

Physiology of skeletal muscle contraction: In brief, the process of skeletal muscle contraction consists of:

(1) Release of acetylcholine in relatively *large amounts* from the synaptic vesicles of the motor nerve into the synaptic cleft as a result of a nerve impulse. Even in the absence of nerve impulse, *minute quantities* of acetylcholine are probably released continuously in the synaptic cleft as testified by the miniature end plate potentials recorded in a resting skeletal muscle.

(2) Acetylcholine released into the synaptic cleft attaches itself to the receptors on the motor end plate. This combination results in the production of a localized depolarization and the development of an end plate potential (E.P.P.) Depolarization is probably due to an influx of sodium and an egress of potassium ions from the motor end plate.

(3) When the end plate potential has achieved a sufficient magnitude, the surrounding area of the muscle fibre membrane is excited, resulting in the development of muscle action potential (M.A.P.) which initiates contraction of the muscle, associated with release of calcium into the sarcoplasm.

(4) Acetylcholine is rapidly hydrolysed by cholinesterase enabling the repolarization of the motor end plate and the muscle fibre membrane. This is achieved probably by reversal of the ionic fluxes. The repolarized muscle is now capable of

responding to a fresh nerve impulse.

Ca^{++} ions seem to play a crucial role in excitation - contraction (E-C) coupling in all muscle types. However, the source of these calcium ions varies in different muscle types and under different experimental conditions. Thus, in most vertebrates and invertebrate smooth muscles, calcium ions bound to the inner surface of the cell membranes are the main source of Ca^{++} for coupling. Cardiac muscles use mainly extra-cellular calcium ions while skeletal muscle uses mainly t-tubular membrane bound calcium for coupling. However, in both these muscles the amount of calcium that enters the myoplasm from these sources is inadequate to complete the coupling process and an amplification system consisting of a Ca^{++} release from the sarcoplasmic reticulum (SR) is required. Drugs can modify this calcium triggered calcium release from the SR in the E-C coupling process in both skeletal and cardiac muscle.

The peripheral skeletal muscle relaxants can be classified according to their mode of action into following groups:

I. Agents acting by competitive blockade of acetylcholine at the motor end plate, e.g. d-tubocurarine, alcuronium, atracurium, vecuronium and gallamine.

II. Agents acting by persistent depolarization of the motor end plate and the muscle fibre membrane e.g. succinylcholine.

I. Drugs acting by competitive blockade:

d-TUBOCURARINE (Tubarine) : This is the dextrorotatory, quaternary ammonium alkaloid obtained from the plant *Chondrodendron tomentosum*, indigenous to the Western Amazon region, and plants of the *Strychnos* species (mainly *Strychnos lethalis*) from Eastern Amazon region of South America. Crude curare is a dark-brown to black gummy mass of resinoid character, soluble in water. The letter 'd' stands for dextro, while the prefix 'tubo' is derived from the fact that crude curare was stored and transported by the South American Indians in bamboo tubes.

Curare was mainly used as an arrow poison by the South American aborigines. Although the mechanism of action of curare was studied by Claude Bernard as early as in 1856, the pure alkaloid was isolated by King only in 1935.

Pharmacological actions:

(a) **Skeletal muscle:** d-Tubocurarine, on parenteral administration, initially produces motor weakness followed by flaccid paralysis. Small, rapidly moving muscles of the fingers, toes, ears and eyes are affected first, making it impossible to perform delicate motor tasks and producing diplopia, slurred speech and difficulty in swallowing. The muscles of limbs, neck and trunk are affected later, followed by the intercostal muscles. Finally, the diaphragm is paralysed and death occurs from hypoxia. Throughout the course of the paralysis, consciousness and sensorium are unaffected. Recovery occurs in the reverse order, the diaphragm recovering first and the small muscles recovering last. d-Tubocurarine combines with the cholinergic receptors on the motor end plate and thus blocks the action of acetylcholine by competitive blockade. It has no effect on elaboration or release of acetylcholine by the motor nerve. The muscle paralysed by d-tubocurarine still responds to direct electrical stimulation, showing that the drug selectively acts in the region of the motor end plate. If the concentration of acetylcholine in the synaptic cleft is increased either by augmenting its release (stronger electrical stimulation of the motor nerve) or inhibiting its destruction (administration of an anticholinesterase drug), d-tubocurarine blockade is reversed.

(b) **Autonomic ganglia:** In high concentrations, d-tubocurarine can produce blockade of the autonomic ganglia after brief initial stimulation.

(c) **Histamine release:** d-Tubocurarine can produce histamine release from tissues. This may occasionally cause bronchospasm, increased salivary, tracheobronchial and gastric acid secretions and contributes towards production of hypotension. These effects can be inhibited by antihistaminic drugs.

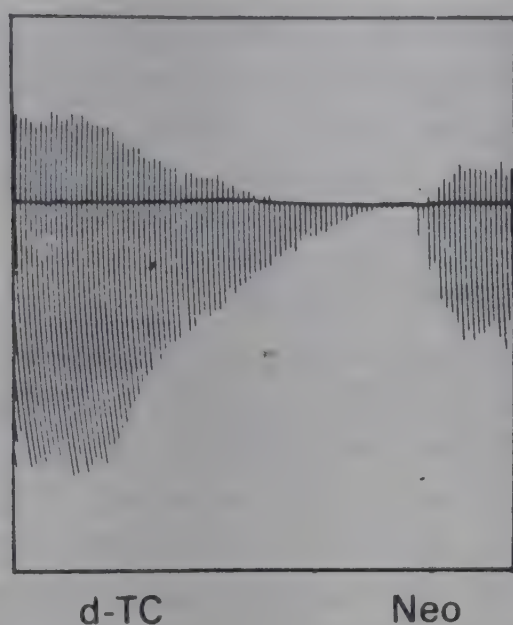


Fig. 18.1: Blocking effect of d-tubocurarine (d-Tc) on electrically stimulated rat phrenic nerve diaphragm preparation. Note the quick recovery following the addition of neostigmine (Neo).

(d) Cardiovascular system : In therapeutic doses, d-tubocurarine has no significant effect on cardiovascular system. Large doses administered rapidly in man, however, may produce a precipitous fall in blood pressure.

Absorption, fate and excretion: d-Tubocurarine, being a quaternary ammonium compound, is not significantly absorbed from the gastrointestinal tract unless used in large doses. The drug is well absorbed on intramuscular administration and is widely distributed in tissues. It is concentrated at the neuromuscular junction. The drug owes its brief duration of action probably to its rapid redistribution. About 33 per cent of the parenterally administered drug is eliminated unchanged in urine within 24 hours. On repeated administration, the drug is capable of producing cumulative toxicity. The metabolic fate of dimethyl tubocurarine is similar to that of d-tubocurarine but the drug has a slightly longer duration of action.

On intravenous administration of a therapeutic dose, skeletal muscle paralysis with tubocurarine becomes discernible within 1 to 1½ minutes, the peak effect is obtained within 5 to 7 minutes and the action persists for 25 to 40 minutes.

The drug does not cross the blood-brain or placental barrier. It is, therefore, devoid of central nervous system effects and may also be employed

in obstetric practice.

Reduced blood flow to the muscle and impairment of hepatic and renal function prolong the tubocurarine action, by interfering with its elimination from the body.

Adverse reactions: Various factors are known to influence the skeletal muscle paralysis induced by d-tubocurarine. The important ones are :

(i) Respiratory acidosis is associated with high plasma levels of d-tubocurarine and prolongation of the neuromuscular blockade. It is important, therefore, to prevent hypercarbia during d-tubocurarine usage. Respiratory alkalosis, on the other hand, results in low plasma levels of the drug and a prompt recovery.

(ii) Increased temperature, hypokalemia and conditions like myasthenia gravis enhance the paralytic effect of d-tubocurarine.

(iii) The general anaesthetic agents ether, halothane, methoxyflurane, isoflurane and enflurane have a synergistic action with d-tubocurarine and other competitive blocking agents; so do aminoglycosides, tetracyclines, polymyxine, clindamycin and lincomycin. The other drugs with similar effect are trimethaphan, opioid analgesics, propranolol, corticosteroids, digitalis, chloroquine, catecholamines and diuretics.

The important adverse reactions include:

(a) **Hypoxia and respiratory paralysis:** This should be treated with positive pressure artificial respiration with oxygen and maintenance of a patent airway till adequate recovery occurs. Neostigmine methyl sulphate, 1 to 3 mg., along with 0.6 to 1.2 mg. of atropine should be administered cautiously. Cardiac arrest, which is liable to occur with neostigmine-atropine combination, however, must be closely watched for. Neostigmine, though countering skeletal muscle paralysis can enhance the bronchospasm, hypotension and hydrochloric acid secretion produced by d-tubocurarine.

(b) **Hypotension:** This usually responds to i.v. fluids. Antihistaminics are also useful to counter bronchospasm and peripheral vasodilatation produced by release of histamine.

(c) **Miscellaneous:** There may be a regurgitation of gastric juice into the oesophagus due to paralysis of the oesophageal sphincter and the diaphragm, leading to oesophageal ulceration.

Preparations and dosage:

(i) Tubocurarine injection I.P. is available in 10 ml. and 20 ml. vials containing 3 mg. per ml. of d-tubocurarine chloride in water. Dose: 6 to 10 mg. initially by intravenous route. The drug may be repeated as per requirements.

(ii) Dimethyltubocurarine iodide (Metubine iodide) is administered intravenously, the initial dose being 3 mg. followed by 1 mg. after 15 minutes, if required.

ALCURONIUM CHLORIDE: This compound is synthesized by structural modifications of *C. toxiferine* - I, another alkaloid with curarizing properties derived from *Chondrodendron tomentosum* and *Strychnos toxifera*.

Alcuronium chloride is a non-depolarizing skeletal muscle relaxant with a speed of onset and duration of action similar to those of d-tubocurarine but is effective in smaller doses. The toxic effects of this compound are similar to those of d-tubocurarine and are reversed by anticholinergic agents. It has an advantage over d-tubocurarine in that it is less likely to release histamine.

PANCURONIUM is a synthetic compound belonging to bis-quaternary ammonium steroids and is about five times as potent as d-tubocurarine as a competitive neuromuscular blocking agent. It has a quicker onset of action and probably does not cause release of histamine. The usual i.v. dose is 0.04-0.08 mg/kg. of bromide salt. It increases the heart rate and the blood pressure and hence, it is preferred in patients with shock.

ATRACURIUM has properties and duration of action similar to those of pancuronium. However, it can be given safely to patients with renal and hepatic impairment, as its metabolism is not altered in these two conditions.

VECURONIUM: This new compound has properties similar to those of atracurium but has shorter duration of action than pancuronium. It is not eliminated by the kidneys and is relatively free of action on the cardiovascular system. It does not produce significant ganglionic or vagal blockade. Further, it does not appear to liberate histamine and its action is promptly antagonized by neostigmine. It is available as bromide salt and is given in the dose of 80-100 µg/kg.

GALLAMINE (Flexedil) : Gallamine is a synthetic, quaternary ammonium compound with curare-like actions.

Pharmacological actions: Gallamine has a similar mechanism of action like d-tubocurarine. The drug, however, is a less potent skeletal muscle relaxant. Unlike d-tubocurarine, gallamine in therapeutic doses blocks the parasympathetic ganglia and has also a weak but highly selective cardiac vagolytic effect. This may lead to tachycardia, cardiac arrhythmias and occasionally hypertension. The drug does not release histamine in therapeutic doses.

Absorption, fate and excretion: Gallamine is administered parenterally. It is not significantly absorbed from the gastrointestinal tract. The drug is excreted almost entirely by the kidneys in an unchanged form. The effect of a single intravenous dose is manifested within 1 to 3 minutes and persists for 30 to 40 minutes. Unlike d-tubocurarine, gallamine can cross the placental barrier and should not be used in obstetric practice.

Adverse reactions: Gallamine shares the adverse effects of d-tubocurarine. Like tubocurarine its effect is appreciably prolonged by aminoglycosides, quinine, propranolol. Ether and halothane potentiate its action while use of potassium depleting drugs like diuretics may cause prolonged neuromuscular blockade.

Preparations and dosage: Gallamine injection I.P. contains 40 mg. of gallamine triethiodide in 2 ml. Dose: initially 1 mg. per kg. of body weight intravenously, then 0.5-1 mg/kg as re-

quired at about 40 min. interval.

II. Drugs acting by persistent depolarization:

SUCCINYLBCHOLINE (Scoline, Midarine):

Succinylcholine is a quaternary ammonium compound with a structure resembling two molecules of acetylcholine joined together. It has a short duration of action.

Pharmacological actions:

(a) **Skeletal muscle:** Paralysis of skeletal muscle produced by succinylcholine is preceded by transient muscular fasciculations and twitching, seen usually in the thoracic and abdominal regions. Fasciculations, however, are usually not observed if the drug is administered to an anaesthetized individual. It has been claimed that succinylcholine relaxes the limb and neck muscles in a dose that does not significantly affect respiratory muscles. Transient apnoea is, however, usually observed with the peak effect of succinylcholine. The skeletal muscle paralysis of succinylcholine is enhanced by anticholinesterases like neostigmine and cathodal current.

The mechanism of action of succinylcholine is not definitely established. It is generally accepted, however, that succinylcholine, which is mainly destroyed by the plasma and liver pseudocholinesterase, acts like a partial agonist of acetylcholine and produces skeletal muscle depolarization. This can explain the fasciculations preceding skeletal muscle paralysis with this agent. However, in contrast to acetylcholine, the drug is destroyed much more slowly, being susceptible only to pseudocholinesterase. This causes a prolonged depolarization during which the muscle is insensitive to further impulses and remains paralysed.

Succinylcholine in high doses (3 mg. per kg.) in human beings has been demonstrated to produce a dual block, initially a depolarizing block which later becomes non-depolarizing, and is antagonised by edrophonium. The mechanism of development of non-depolarizing blockade with large doses is not clear.

(b) **Cardiovascular system:** Succinyl-

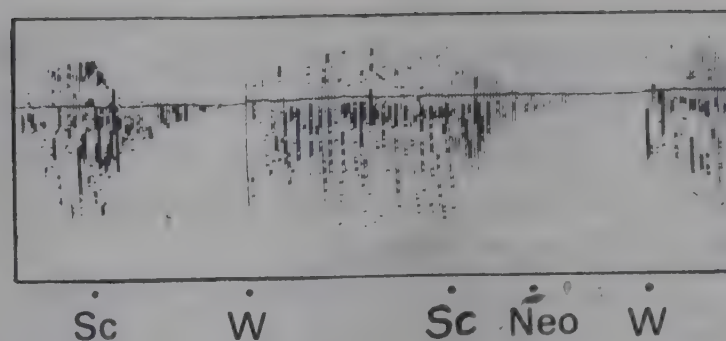


Fig. 18.2 : Blocking effect of succinylcholine (Sc) on electrically stimulated rat phrenic nerve diaphragm preparation. Note the worsening of the block following neostigmine (Neo) and recovery after wash (W).

choline, being a partial agonist of acetylcholine, initially produces hypotension and bradycardia. Repeated drug administration may produce cardiac arrhythmias. Bradycardia and hypotension are usually followed by hypertension and tachycardia which are more persistent. This may be attributed to stimulation of sympathetic ganglia preceding their blockade by high doses of succinylcholine.

(c) **Miscellaneous:** Succinylcholine does not release histamine. Large doses may cause hypotension as a result of muscarinic effect and to some extent by ganglionic blockade. Because of the muscarinic action of succinylcholine, atropine is generally given before its use.

Absorption, fate and excretion: Succinylcholine, administered intravenously, produces fasciculations which last for 10 to 15 seconds. Peak effect develops within 1 to 2 minutes and muscle power recovers within 5 minutes. The drug is hydrolyzed by plasma and liver pseudocholinesterase first to succinylmonocholine which has a weak competitive neuromuscular blocking effect and subsequently to succinic acid and choline. Approximately 10 per cent of the intravenous dose is excreted unchanged in the urine. The drug crosses the placental barrier in insignificant amount and hence, can be used in obstetric cases.

Adverse reactions: Factors influencing the effect of succinylcholine include:

(i) As in the case of d-tubocurarine, infants below the age of 1 and persons suffering from myasthenia gravis, muscular dystrophies, colla-

gen diseases, porphyria, thyrotoxicosis, severe anemia and electrolyte disturbances are more susceptible to the paralytic effect of succinylcholine. Unlike tubocurarine, however, the drug action is not significantly affected by antibiotics and other curarimimetic agents.

(ii) Advanced liver disease is usually associated with reduced plasma cholinesterase levels and such individuals are highly susceptible to succinylcholine.

(iii) Procaine, which is hydrolyzed by plasma pseudocholinesterase, competes with succinylcholine for the enzyme and prolongs the action of succinylcholine.

(iv) Presence of an abnormal plasma pseudocholinesterase (a hereditary defect), having a poor ability to hydrolyse succinylcholine or acquired deficiency of normal pseudocholinesterase as in liver disease predisposes to the development of prolonged apnoea following a normal dose of succinylcholine.

(v) The use of Anti-ChE drugs locally in the eye for glaucoma may permit the absorption of enough drug to potentiate the neuro-muscular blocking effect of succinylcholine.

Metabolic acidosis can also precipitate succinylcholine apnoea. Apart from allergic reactions other important adverse reactions are:

(1) **Cardiac arrest and arrhythmias:** High incidence of cardiac arrhythmias with the use of succinylcholine-halothane combination has been reported. The drug may occasionally produce severe cardiovascular collapse.

In digitalized patients, the effect of digitalis on the cardiac conduction time is enhanced by succinylcholine. Intravenous succinylcholine, therefore, can produce serious ventricular arrhythmias in fully digitalized patients. In the incompletely digitalized patient, succinylcholine can produce the E.C.G. changes characteristic of digitalization.

(2) **Succinylcholine apnoea:** Apnoea lasting for more than 15 minutes is considered abnormal.

It should be treated by artificial respiration and fresh blood transfusion. No antidote is available.

(3) It can rarely trigger the onset of serious malignant hyperthermic crisis in patient receiving ether or halothane.

(4) **Miscellaneous:** Muscle soreness is a fairly frequent complaint following succinylcholine administration.

Preparations and dosage: Succinylcholine chloride injection N.F. is available as 2 ml. ampoules containing 50 mg. of the salt (36.5 mg. of succinylcholine) per ml. Dose: initially 1 mg. per kg. administered slowly by intravenous route followed by supplements of 0.3 mg/kg when needed.

Therapeutic uses of peripheral skeletal muscle relaxants:

(i) **Adjuvant to anaesthesia:** The main use of skeletal muscle relaxants is to promote skeletal muscle relaxation during abdominal surgery, orthopaedic manipulations, and during various brief procedures like laryngoscopy, bronchoscopy and oesophagoscopy. When the procedure involved is of short duration, succinylcholine is obviously the drug of choice. The drug can also counter laryngeal spasm during barbiturate anaesthesia. For prolonged muscular relaxation, d-tubocurarine or gallamine is preferred, the former being the drug of choice for obstetric cases.

(ii) **In electroconvulsive therapy:** Scoline is often administered together with diazepam to protect the patient from injury during electroconvulsive therapy. Barbiturate-muscle relaxant combination may, however, produce respiratory depression and hence prophylactic endotracheal intubation is advised.

(iii) **In spastic disorders:** The peripheral skeletal muscle relaxants have been advocated to overcome the severe spasm of tetanus, athetosis and status epilepticus. Their use, however, involves risk and needs expert supervision.

19 Drug Therapy of Parkinsonism

Parkinsonism as a clinical entity was first described by James Parkinson in 1817. It is a syndrome of varied etiology, the most important features of which are akinesia, muscular rigidity and tremor. Excessive salivation, seborrhoea, mood changes (especially depression) and liver damage may be present in certain patients.

Besides the idiopathic, arteriosclerotic and post-encephalitic forms, the syndrome is seen in hepatolenticular degeneration of Wilson's disease and can be induced by drugs like reserpine, haloperidol, triperidol, chlorpromazine and other halogenated phenothiazines.

Pathophysiology: It is now established that in the idiopathic variety (Parkinson's disease or paralysis agitans), there occurs depigmentation and loss of pigmented neurons in the substantia nigra. These neurons make efferent connections in the putamen, the globus pallidus and the caudate nucleus (i.e. the corpus striatum). As the nigro-striatal neurons are dopaminergic, degeneration of some of them deprives the striatal nuclei of an adequate dopamine (DA) input. This allows cholinergic transmission to predominate in the basal ganglia. The clinical features of parkinsonism are explained by the combination of dopamine deficiency (akinesia) and cholinergic preponderance (tremor and rigidity). Initially, the dopamine deficiency is compensated for by increased synthesis of dopamine by the surviving nigro-striatal neurons and by an increased sensitivity of the striatal neurons to dopamine. Levodopa helps in this compensation by supplying the raw material for dopamine synthesis. Anticholinergic drugs help to diminish the cholinergic preponderance; further, some of them (par-

ticularly benztropine) inhibit active dopamine re-uptake in the striatum and help to increase the local dopamine concentration. In general they are less effective than levodopa in idiopathic parkinsonism which is caused primarily by dopamine deficiency. As the disease progresses (and no drug can halt this), more and more nigro-striatal neurons fall out and even levodopa becomes less and less effective. The disease is progressive and incurable and the treatment is symptomatic, empirical and lifelong.

In drug-induced parkinsonism, the dopamine receptors in the striatum are blocked—there is no deficiency of dopamine. Hence, the condition is not helped by levodopa but is alleviated by omitting the offending drug and by anticholinergics.

Systemic administration of 1-methyl - 4 - phenyl 1,2,3,6 tetrahydro pyridine (MPTP) to experimental animals, including mice and monkeys, results in selective destruction of dopaminergic neurons of the nigrostriatal pathway. The MPTP treated primates represent the best animal model of Parkinson's disease currently available. It has been postulated that Parkinson's disease in humans may be caused by chronic exposure to MPTP-like substances in the environment, combined with effects of aging.

The aims of treatment are :

(a) **Relief of rigidity, tremors and akinesia :** Most of the drugs reduce rigidity more than tremor and akinesia. Tremor, in fact, may be aggravated after reduction in rigidity. Levodopa ameliorates all the clinical manifestations of parkinsonism. Reduction in rigidity and tremor allows the patient more free and easy movements, increases the mobility and boosts up his morale.

Physiotherapy acts as a valuable adjuvant in such cases.

(b) **Correction of mood changes :** Depression is often a marked feature of arteriosclerotic parkinsonism. If the primary drug employed fails to correct it, a tricyclic antidepressant may be administered with beneficial effects. Optimism is infectious and hence, physician's attitude must be one of hope and cheerfulness.

(c) **Treatment of symptoms :** Treatment of symptoms such as excessive salivation and seborrhoea and of complications such as oculogyric or sweating crisis is important.

(d) **Treatment of cause if possible :** Parkinsonism following drugs like phenothiazines and reserpine is completely reversible after stopping the drugs. Reduction in high tissue copper levels associated with Wilson's disease also results in some relief.

The various forms of treatment available are: (i) drug therapy, (ii) physiotherapy and (iii) surgical treatment.

DRUG THERAPY

The drugs used in the treatment of parkinsonism can be classified as :

- (a) Levodopa
- (b) Amantadine
- (c) Miscellaneous drugs :
 - (i) Anticholinergics like atropine and synthetic atropine substitutes e.g. benzhexol, cycrimine, procyclidine, biperiden and benzotropine.
 - (ii) Antihistaminics : Diphenhydramine, promethazine, orphenadrine and chlorphenoxan.
 - (iii) Phenothiazines : Ethopropazine.
 - (iv) Bromergocryptine.

The mechanism by which various drugs except l-dopa relieve rigidity and tremor is unknown; but it may be possibly related to their anticholinergic actions. There is now substantial evidence that acetylcholine and dopamine are excitatory and inhibitory neurotransmitters in the corpus striatum.

In parkinsonism, the dopaminergic system appears to be impaired so that the balance is disturbed. Anticholinergic drugs like atropine probably act by restoring this balance.

(a) **LEVODOPA** (Larodopa, Levopa, Avodopa): Levodopa itself is pharmacologically almost inert and produces its central and peripheral effects by being first converted enzymatically to dopamine. Dopamine itself is of no value in parkinsonism as it does not cross the blood-brain barrier.

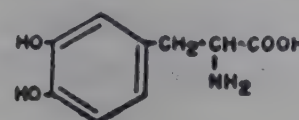


Fig 19.1 : Levodopa

Pharmacological actions : The pharmacological effects of levodopa on muscle tone and movement are seen exclusively in patients with parkinsonism but not in normals. It can be called a universal antiparkinsonian drug as it improves all the manifestations of parkinsonism. Akinesia responds first, followed by rigidity and tremor. Tremor may, however, be initially aggravated in some patients. Other manifestations such as seborrhoea, sialorrhoea and aphonia also improve. The drug improves mood, memory and makes the patients more alert and interested in themselves and in their surroundings. The subjective improvement and the improvement in the general motor performance of the patient far surpass the more modest improvement in the conventional physical signs of parkinsonism. Once achieved, the beneficial effects of l-dopa can be maintained for prolonged periods by smaller maintenance doses. About 30% of the patients show 'impressive' improvement whereas another 30% show 'worthwhile' improvement. Patients with idiopathic parkinsonism need larger doses than those with post-encephalitic parkinsonism. In general younger patients with milder symptoms derive greater benefit than elderly, debilitated patients

who cannot tolerate full doses because of adverse effects. Improvement of parkinsonian symptoms arising from manganese poisoning has been reported. *Drug-induced Parkinsonism does not respond at all to levodopa.* Transient, rapid deterioration in all symptoms (akinesia, tremor and rigidity), called 'on-off' phenomena, developing in minutes and clearing up spontaneously in 1-6 hours has been reported in patients on prolonged treatment with levodopa. These correlate with fluctuations in the plasma levels of levodopa.

Levodopa in small doses markedly increases the cardiac contractile force and reduces the arterial pressure. Since these effects do not occur following prior administration of decarboxylase (DC) inhibitors such as carbidopa which does not cross the blood brain barrier, it appears that levodopa produces its cardiovascular effects by slowly releasing DA into the circulation. Dopamine acts on the cardiovascular system by:

(i) stimulating beta-adrenergic receptors in the heart (positive inotropic action); this effect can be blocked by beta-adrenergic blocking agents.

(ii) stimulating alpha-adrenergic receptors in blood vessels to produce vasoconstriction. Thus, large doses of levodopa may cause rise in blood pressure which can be countered by alpha-adrenergic blocking agents such as phentolamine; and

(iii) acting on specific dopaminergic receptors to cause renal and mesenteric vasodilatation which causes fall in blood pressure following small doses of levodopa.

Levodopa inhibits prolactin secretion in man. The increase in plasma growth hormone level which occurs when levodopa is given to normal persons is minimal or absent in patients with parkinsonism.

Absorption, fate and excretion : The drug is rapidly absorbed when given orally with peak plasma levels at 1/2-2 hours. The plasma $t_{1/2}$ is 1-3 hours. As more than 95% of orally taken levodopa is rapidly decarboxylated peripherally in the lumen of the G.I. tract, liver (first pass effect) and other tissues to dopamine, very little

(less than 1%) is left to enter the C.N.S. Hence, large doses of levodopa are needed to permit enough to penetrate into the brain to raise its dopamine content. The blood levels of levodopa can be increased by inhibiting the decarboxylase (DC) enzyme present in the intestines and other tissues by using DC inhibitors. Since such DC inhibitors do not easily penetrate the blood-brain barrier, conversion of levodopa to dopamine is not prevented in the brain. Pyridoxine accelerates its peripheral decarboxylation as the decarboxylase is pyridoxine dependent. The drug is excreted in the urine partly unchanged and partly as dopamine and its principal metabolite homovanillic acid (HVA). Some of the drug is converted to noradrenaline since the urinary excretion of vanilmandelic acid (VMA) and 3 methoxy-4-hydroxy phenylglycol (MHPG) also increases.

Adverse reactions: These occur in a large number of patients and almost every patient may show some adverse effect. These are :

(a) *Gastrointestinal system* : Nausea, vomiting and anorexia occur very commonly. They are of central origin (action on CTZ) and are minimized by taking levodopa with food (which reduces its absorption) and by increasing the dose slowly when initiating therapy.

(b) *Behavioural toxicity*: This includes depression with attempted suicide, agitation, confusion, restlessness, hallucinations and delusions. The drug exacerbates latent or active psychotic states both organic and functional. These disturbances make it necessary to abandon treatment. Patients with history of psychiatric disturbances should not be treated with levodopa.

(c) *Cardiovascular system*: It causes postural hypotension, generally asymptomatic. It is of central origin and is not prevented by DC inhibitors. It can also cause palpitation, sinus tachycardia, increased A-V conduction and ventricular arrhythmias; these can be countered by a DC inhibitor and by beta-adrenergic blocking agents such as propranolol. Tolerance develops over weeks to postural hypotension as well as to the cardiac effects of levodopa.

(d) *Central nervous system*: On prolonged therapy, abnormal movements involving head, neck and sometimes even the extremities may occur. They are usually choreiform in nature and can be quite disturbing and even incapacitating to the patient. Unfortunately, they coincide with optimum therapeutic effect and correlate with the duration of therapy and with the dosage of levodopa. They are not prevented by a D.C. inhibitor. They are abolished by pyridoxine which, however, reduces the efficacy of levodopa.

Parkinsonian patients commonly suffer from insomnia but do not complain of it because their daytime symptoms are far more severe. An improvement in their daytime symptoms can make these patients more acutely aware of their insomnia which, in fact, is neither improved nor worsened by levodopa.

(e) *Miscellaneous*: Some patients may show positive Coomb's test, though hemolytic anemia has not been reported. Blood urea nitrogen and serum SGOT may show a transient rise. Rise in plasma cholesterol levels and a decrease in carbohydrate tolerance have been reported in some patients during prolonged treatment.

The urine is red coloured when passed and becomes dark on exposure to air or alkali. The urine gives a false positive test for ketone bodies with the dip-stick test.

Of these adverse effects, nausea, vomiting and postural hypotension occur early in therapy. Most patients develop tolerance to them. Abnormal involuntary movements and psychiatric disturbances occur on long term treatment with optimum doses. As tolerance does not develop to these symptoms, they prove dose-limiting in most patients.

In view of its cardiac toxicity, the drug should be used cautiously in patients with history of myocardial infarction and with ECG evidence of ectopic activity. Similarly, sympathomimetic amines like adrenaline and isoprenaline should be avoided in patients receiving levodopa. The drug should be withdrawn prior to administration of anaesthetic agents like cyclopropane and halothane. Administration of MAO inhibitors may

precipitate severe hypertension in patients on levodopa therapy; this can be treated by phenolamine. An MAOI should be stopped at least two weeks before initiating levodopa therapy.

Reserpine, phenothiazines and even small doses of pyridoxine counter the effects of levodopa and should not be used along with it. Anticholinergics, barbiturates, benzodiazepines, tricyclic antidepressants, diuretics, oral hypoglycemic agents, antibiotics, trinitrin, digoxin, propranolol and anti-arrhythmic agents may, however, be safely used along with levodopa, if necessary. Methyldopa intensifies the adverse effects of levodopa. Anticholinergics increase the degradation of levodopa by prolonging its stay in the intestines. Hence, they should be taken 2 hours before levodopa if the two are used concurrently.

Preparation and dosage: Levodopa is available as 0.5 g. tablets. The initial dose of levodopa is 125 mg. twice daily. The total daily dose is progressively increased once in 3-4 days till satisfactory control is achieved or adverse effects appear. The majority of patients need 2-6 g. per day in four divided doses. As the drug has a short plasma half-life, frequent dosage is necessary to maintain an even therapeutic effect and to minimize certain adverse effects. Most patients show a good therapeutic response in 2-4 weeks but some may take as long as 3-4 months. The total daily dosage should not exceed 8 g. *Concurrent administration of a DC inhibitor permits a 75% reduction in the daily dose of levodopa.*

Decarboxylase (DC) inhibitors : By themselves, these drugs are largely pharmacologically inactive. However, the concurrent administration of an extracerebral DC inhibitor that does not enter the brain decreases the peripheral decarboxylation of levodopa. This endows the following advantages on levodopa therapy : (1) The effective dose of levodopa can be reduced by as much as 75%. (2) Nausea and vomiting are largely prevented; so also the cardiac effects. (3) This permits more rapid increase in the dosage to optimum levels. (4) Pyridoxine does not antagonize the effects of levodopa any more. (5) The control of symptoms is smoother and wide diurnal

fluctuations are avoided. (6) The number of divided doses per day can be reduced without loss of control. More patients seem to achieve a greater degree of benefit.

Postural hypotension, abnormal involuntary movements and psychiatric disturbances are not prevented or eliminated by concurrent use of DC inhibitors.

Carbidopa and benserazide hydrochloride are the two DC inhibitors currently available in combination with levodopa. Carbidopa (methyl dopa hydrazine) is present in the tablets (Sinemet) in amounts 1/10th (10 mg) that of levodopa (100 mg) and benserazide in amounts 1/4th (25 mg) that of levodopa (100 mg).

SELEGILINE (Deprenyl) : There are at least two types of monoamine oxidase inhibitors: type A causes oxidative deamination of noradrenaline and serotonin; type B acts on dopamine in human platelets and brain. Deprenyl is a selective irreversible inhibitor of MAO-B. By itself, it has no antiparkinsonian activity. Given along with levodopa or with levodopa-carbidopa combination, it prolongs the duration of the action of levodopa. Further, it diminishes the incidence of on-off phenomena. It is believed to act by increasing the concentration and storage of dopamine within the striatum. The major adverse effect is an increase in the incidence of dyskinesias. It is available as 5 and 10 mg. tablets. The daily dose is 5-10 mg. It may be used on alternate-day basis, as its action is prolonged.

Recent studies indicate that deprenyl given 5 mg. twice daily, significantly delays the development of disability in parkinsonism.

(b) **AMANTADINE (Symmetrel, Amantrel)**: This drug, developed originally as an antiviral agent, has been found to ameliorate akinesia, rigidity and tremor in parkinsonism. Its therapeutic efficacy in this respect is 15-20 per cent that of levodopa but slightly higher than that of anticholinergics. But, it produces a more rapid response (2-5 days) than levodopa and its dosage is

easier to adjust. It is believed to act by liberating dopamine from the residual intact nerve endings. The drug is well absorbed orally and is excreted unchanged in urine. Its adverse effects are similar to those of anticholinergic drugs whose adverse effects it potentiates. In toxic doses, it causes convulsions, mania and hence, it should be used cautiously in epileptics. In general, the drug is well tolerated and is reported to produce fewer adverse reactions than levodopa and anticholinergic drugs. It is administered in the dose of 100 mg per day, increased to 100 mg twice a day after 7-10 days. As restlessness is one of its major adverse effects, the second dose should not be taken late in the day. With larger doses, the adverse reactions increase disproportionately. It should be noted that amantadine is not useful in drug induced parkinsonism. Addition of amantadine in patients receiving near maximum benefit from levodopa causes little further improvement. Further, amantadine seems to lose a part of its efficacy after a few weeks of continued administration. The best way of using this drug may be to give it for 2-4 weeks at a time, whenever extra therapeutic support is desired.

(c) **Miscellaneous drugs**: These include the belladonna alkaloids, synthetic atropine substitutes, antihistaminics, phenothiazines and bromergocryptine.

Belladonna alkaloids are discussed here as often they are the only drugs patients can afford for prolonged periods. Benzhexol is discussed in detail as a prototype of the synthetic atropine substitutes. The salient features of other drugs are shown in Table 19.1. They differ from benzhexol only in the duration of their action and in the individual toleration of them by patients.

Antihistaminics and phenothiazines used also have anticholinergic action in common and therefore, share certain atropine-like adverse effects.

Bromergocryptine is discussed separately because of its novel mode of action.

BELLADONNA ALKALOIDS: The pharma-

Table 19.1 : Miscellaneous drugs for parkinsonism

Drug and Preparations	Dosage	Comments
Synthetic Atropine Substitutes		
Benzhexol (Pacitane) Tab. 2 and 5 mg.	Initial 2 mg/day increased upto 20 mg/day	See text.
Cycrimine HCl (Pagitane) Tab. 1.5 and 2.5 mg.	Initial 5- 10 mg/day. Increased upto 20 mg/ day	Claimed to produce fewer adverse effects than benzhexol
Procyclidine HCl (Kemadrine) Tab. 2 and 5 mg.	Initial 7.5 - 10 mg/ day. Increased upto 40-60 mg/day	Similar to cycrimine
Biperiden HCl (Akineton) Tab. 2 mg. Inj. Biperiden lactate 5 mg/ml.	Initial 6 - 8 mg/day	Similar to cycrimine
Benztropine mesylate (Cogentin) Tab. 0.5, 1 and 2 mg. Inj. 2 mg/2ml.	Initial 1.5 - 3 mg/day	A potent blocker of re-uptake of dopamine. Has a prolonged action and a sedative effect
Antihistaminics		
Diphenhydramine HCl (Benadryl) Capsules 25 and 50 mg.	Initial 50 -100 mg/day	Relieves rigidity but not tremor or sialorrhoea, well tolerated, causes drowsiness and giddiness
Promethazine HCl (Phenergan) Tab. 10, 25 and Inj. 25 mg.	25 mg. I.V. followed by 25 mg by mouth if necessary	Especially useful in rapidly controlling acute dystonic drug-induced reactions. Causes drowsiness
Orphenadrine HCl (Disipal) Tab. 50 mg. and Inj. 25 mg/ml.	Initial 150 mg/day Increased upto 300 mg.	Similar to diphenhydramine Elevates mood

cology of the belladonna alkaloids has been discussed in Chapter 16. Both atropine and hyoscine can relieve, to some extent, the rigidity and tremor and some beneficial effect regarding hyperhidrosis, seborrhoea and sialorrhoea also occurs.

Atropine is usually started orally in a small dose of 0.5 mg. twice or thrice daily, and the dose is gradually increased till mild adverse effects are produced. With the development of tolerance to belladonna, another drug is added to maintain the initial improvement. These agents are more useful in younger subjects.

BENZHEXOL HYDROCHLORIDE (Trihexyphenidyl, Artane, Pacitane): Benzhexol belongs to the class of synthetic atropine substitutes. These compounds have weaker peripheral anticholinergic actions than belladonna alkaloids. Benzhexol is an effective and the most commonly used drug among the synthetic atropine substitutes.

Pharmacological actions: The drug is useful in controlling muscular rigidity, tremor, sialorrhoea and seborrhoea. It affects the mood favourably. In patients with excessive muscular rigidity, however, the drug may increase tremor

while reducing rigidity. In large doses, the drug produces cerebral stimulation.

Absorption, fate and excretion: Benzhexol is well absorbed on oral administration. The drug rapidly disappears from the tissue but its fate is unknown.

Adverse reactions: The drug is free from serious adverse effects; however, atropine-like side effects may develop even in therapeutic doses in 10 to 20 per cent of patients. These include xerostomia, blurred vision, nausea, dizziness and restlessness. The drug may precipitate urinary retention in the presence of prostatic enlargement. Overdosage causes confusion, hallucinations and delirium.

Preparations and dosage: It is available as 2 and 5 mg. tablets and 5 mg. sustained release capsules. The initial dose of the drug is 1 to 2 mg. and is increased gradually upto 10 to 30 mg. per day to obtain the optimum effect. A single dose of the sustained release capsule maintains the effect for 15 hours and this preparation may be employed after initial stabilization. The central stimulation produced by the drug is usually countered by combining it with a agent like diphenhydramine.

Therapeutic use: Before the advent of levodopa, benzhexol was termed as a 'universal' drug in the treatment of parkinsonism as it controls to some extent, all the signs in this condition. It can be used even in the presence of hypertension and cardiac disease.

BROMERGOCRYPTINE (Parlodel): This is an ergot preparation which has a specific dopamine receptor-agonist action. It is capable of crossing the blood brain barrier. Unlike levodopa, it does not have to be converted to an active metabolite. Though it has been found useful in the treatment of parkinsonism it is slower acting than levodopa. It is used in the dose of 2.5 mg. twice a day to begin with and the dose is slowly increased to a maintenance dose of 20-150 mg per day. This dose is almost ten times that required to suppress galactorrhoea. Its other important pharmacologi-

cal actions and adverse effects are described in Chapter 62.

Principles of drug therapy: Introduction of levodopa was a landmark in the therapy of parkinsonism. Unlike the older drugs, it alleviates all the three cardinal features of this disease, namely rigidity, tremor and akinesia. However, the variety and frequency of adverse effects, making continued close supervision mandatory, and the high cost put serious limitations on its routine use in all cases in poor countries. The physician who prescribes levodopa must be willing to supervise the patient closely for prolonged periods and be familiar with its adverse effects and its pharmacological incompatibilities with other commonly used drugs. Lastly, in course of time levodopa becomes less effective. Its effectiveness would appear to be restricted to about 5 years, whether the drug is started early or late in the disease.

The synthetic atropine substitutes are still important in the treatment of parkinsonism, benzhexol being the most effective drug from this group. Treatment should be started with a small dose which should be increased gradually. As maximally tolerated doses do not give much more benefit than slightly smaller and better tolerated doses, no attempt should be made to push the dose to the limit of tolerance. Some patients do not improve adequately on this drug or the initial improvement is lost due to the development of tolerance. In such cases, another synthetic atropine substitute should be tried or a drug from the other groups (antihistaminic, phenothiazines or levodopa) may be added to benzhexol. The change over to a new drug should be gradual and overlapping.

Not all patients with parkinsonism need drug therapy. Relatively inactive patients with minimal disease and no disability may be treated with physiotherapy alone. The anticholinergic drugs may be used in patients with mild disease, who have no contraindication to their use. They may also be used in patients who cannot tolerate

levodopa. Finally, they can be used in combination with either amantadine or levodopa. It is however, best to avoid combining an anticholinergic agent and levodopa if there is history of psychosis. The antihistaminic drugs are particularly useful in elderly patients with mild disease, who cannot tolerate the anticholinergic drugs. Further, they help to counter the insomnia in patients on levodopa or anticholinergics. Amantadine is a useful alternative to anticholinergic drugs in patients with mild parkinsonism. It can also be used as an adjunct in patients who are unable to tolerate full doses of levodopa. Levodopa is best reserved for symptomatic patients who are incapacitated by restricted locomotion due to severe disease. Further, as the duration of effectiveness of levodopa therapy seems to be restricted to about 5 years, it may be better to start levodopa later than earlier in the course of the disease. Some physicians would like to add carbidopa from the start; others would reserve it for later stages of therapy. Bromocriptine is best reserved for patients with severe disease who cannot tolerate levodopa and for those who get frequent on-off phenomena. Deprenyl is also similarly reserved for this latter group of patients.

Regular treatment with the standard drug therapy can prevent oculogyric crises which are rare except in post-encephalitic parkinsonism. Addition of dexamphetamine in the dose of 5-10 mg, once or twice daily offers additional protection against oculogyric crises; *but, dexamphetamine must not be used along with levodopa*. Orphenadrine and trihexyphenidyl are effective in preventing and treating the rarer sweating crises. Depression is common in parkinsonism and can especially occur in patients on levodopa. Its relief with tricyclic antidepressants like imipramine can release unexpected powers of movement for the patient. Sialorrhoea is usually controlled by atropine substitutes. If dryness of the mouth is bothersome, it can be relieved by the use of hard candy. Paralysis of accommodation responds well to daily instillation of 0.5% physostigmine eye drops and seborrhoea to local application of sulfur lotion.

The patient must be warned against the sudden cessation of drug therapy as this may prove fatal. Acute infections and surgery tend to cause rapid deterioration in the health of a patient with parkinsonism. Hence, surgery should be avoided unless it is absolutely necessary. Further, levodopa should be continued post-operatively and during an infective illness.

Drug-induced parkinsonism responds satisfactorily to drug withdrawal and to the anticholinergic drugs but not to levodopa.

Limitations of drug therapy:

(1) Drugs do not cure the disease nor affect its course. All that can be expected from them is 20 to 70 per cent symptomatic improvement in 60-80 per cent of the patients. Tremor is not much helped by these drugs with the exception of levodopa.

(2) Tolerance develops with most of the drugs.

(3) Older patients tolerate the drugs less well than younger individuals.

(4) Drugs with prominent anticholinergic actions must be used cautiously in patients with glaucoma and prostatic enlargement.

(5) This drug is not recommended during pregnancy, lactation or in children below 12 years.

(6) Levodopa therapy is expensive and the drug has many adverse effects.

Physiotherapy: Heat and gentle massage help to relax the rigid muscles. Physical activity just short of fatigue in a patient treated with drugs makes all the difference between an incapacitated, depressed and sometimes bedridden patient and one who is well-adjusted, ambulatory and able to take care of himself.

Surgery : Selective destructive lesions of the ventrolateral nucleus of the thalamus have been shown to control tremor, and to a lesser extent, rigidity, without causing paralysis. Patients who are under sixty years of age and have essentially unilateral disease, especially tremor, are likely to benefit from such procedures. Bilateral parkinsonism, severe akinesia and mental deterioration are contraindications to any operative treatment.

DRUG-INDUCED EXTRAPYRAMIDAL REACTIONS

Certain drugs used in therapeutics (phenothiazines, butyrophenones, thioxanthenes, metoclopramide, reserpine, methyldopa and levodopa) cause a variety of extra-pyramidal reactions. These reactions can be broadly grouped into four syndromes:

(1) *Parkinsonism*: It is almost indistinguishable from idiopathic parkinsonism but tremor is an infrequent feature. It is said to occur more often in women than in men and has been reported with all drugs mentioned above except levodopa.

(2) *Akathisia* (not to sit): In this syndrome, the patient exhibits a compulsive motor restlessness, is constantly on the move and is apprehensive. It needs to be distinguished from psychotic agitation which it resembles, because unlike the latter it is aggravated by an increase in the dose of the antipsychotic drugs. It has been reported with the antipsychotic phenothiazines and with metoclopramide.

(3) *Acute dystonic reactions*: These are characterized by painless, spasmodic contraction of one or more muscle groups resulting in trismus, torticollis, opisthotonus or oculogyric crisis. They are seen mainly with phenothiazines and butyrophenones.

(4) *Tardive dyskinesia*: This syndrome, reported to occur late during phenothiazine therapy, develops gradually and consists of involuntary movements such as repetitive sucking, smacking

of lips, grimacing and movements of the tongue and extremities. Old age, prior brain damage, schizophrenia and cerebral anoxia seem to predispose to it. It may persist indefinitely after stopping the drug that caused it and is assumed to be related to dopamine receptor supersensitivity.

In practice, such episodes of extrapyramidal reactions can be prevented by (1) using less toxic drugs such as benzodiazepines for sedation or cyclizine to treat vomiting; (2) prescribing the antipsychotic drugs in the minimal effective doses, and (3) concurrent administration of low doses of antiparkinsonian drugs like benzhexol along with anti-psychotic drugs. Anticholinergic drugs, however, fail to prevent the development of tardive dyskinesia. Keeping a vigilant watch for the adverse reactions during therapy is mandatory.

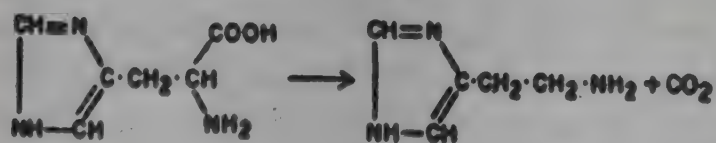
Treatment: (1) At the first sign of extrapyramidal reactions, reduce the dose of the offending drug. If possible, replace it with a less toxic drug from the same group or a drug from another group. (2) Drug induced parkinsonism is treated by adding an antiparkinsonian drug of the anticholinergic group. *Levodopa and amantidine are not effective*. (3) Acute dystonic reactions respond well to an intravenous injection of 25 mg. of promethazine, followed by 25 mg. orally; and to diazepam 5 mg. I.V. (4) Many other drugs such as reserpine and tetrabenazine have been claimed to be useful in cases of "tardive" dyskinesia. However, no reliably effective drug is available at present for this disorder.

Section V : Other Biogenic Amines and Polypeptides

20 Histamine and Antihistaminic Drugs

Histamine ('tissue amine'), a potent biogenic amine, was synthesized even before its isolation from plants and animals, by Windaus and Vogt in 1907. The compound was isolated from ergot extracts by Barger and Dale in 1910 and reports regarding its pharmacological actions were published by Dale and Laidlaw in 1910-1911. The role of this extremely potent substance in the genesis of allergic and anaphylactic manifestations was forecast by the brilliant work of Lewis but even now, the exact biological functions of this compound have not been determined.

Distribution and synthesis: Histamine, an imidazole compound, is widely distributed in plant and animal tissues, and is also present in the venom of bees and wasps. In the mammals, it is formed by decarboxylation of the amino acid histidine. This reaction is catalysed by an enzyme, histidine decarboxylase. Histamine is also synthesized by the microflora in the gastrointestinal tract from dietary histidine. Very little, however, reaches the circulation as most of what is absorbed is catabolized in the intestinal wall and the liver.



Histidine

Histamine

Fig 20.1 : Biosynthesis of histamine

In the body, histamine is present in various biological fluids, and in platelets, leucocytes, basophils and mast cells. A major portion of histamine is stored in mast cells and circulating basophils. These cells show the presence of his-

tidine decarboxylase, and also contain specialized granules, wherein histamine is stored in a metabolically inactive form. In the mast cells of majority of animals, histamine is stored along with heparin, and in rodents, along with 5-hydroxytryptamine. Animal lung is particularly rich in histamine, and rupture of mast cells releases free histamine into the circulation. Tissues devoid of mast cells e.g. human epidermis and gastrointestinal mucosa also contain a significant concentration of histamine. Within the gut, the histamine concentration is highest in the stomach wall and it diminishes progressively upto colon. In the central nervous system, the area postrema, the mast cells of the pituitary stalk and the hypothalamus contain significant amounts of histamine.

Broadly speaking, tissue histamine in man and the carnivores has its origin in the gut, whereas in the rodents it is formed in the tissues themselves.

Mechanism of action: The present evidence indicates that histamine acts on three types of receptors, H_1 , H_2 and H_3 .

Stimulation of H_1 receptors produces smooth muscle contraction, increased vascular permeability and mucus secretion. It is associated with increase in intracellular cyclic guanosine 3', 5' monophosphate (cGMP). In the tissues, histamine serves as a chemotactic agent for neutrophils and eosinophils. H_1 receptor effects are competitively blocked specifically by the conventional antihistaminics such as mepyramine.

Activation of H_2 receptors, on the other hand, increases the gastric acid secretion in humans and in guinea pigs and the contraction rate of the isolated right atrium in guinea pigs. This is asso-

ciated with a decrease in cGMP but an increase in cAMP in the cells. These effects are not blocked by the conventional antihistaminics but are specifically blocked by H₂ receptor antagonists such as cimetidine. These antagonists also block the effects of the gastrin analogue pentagastrin. Impromidine is a potent H₂ receptor agonist and behaves as a competitive antagonist at the autoinhibitory receptors.

Both H₁ and H₂ receptors appear to be involved in vascular dilatation and in edema formation.

For H₃ receptors see later.

Pharmacological actions of histamine: The important pharmacological actions of histamine are:

Cardiovascular system :

(a) *Blood vessels* : Histamine produces contraction of majority of large blood vessels and arterioles; however, there is a considerable species difference. Thus, the constrictor effect dominates in herbivores like rabbits and guinea pigs, while in man, cat and dog, this effect appears to be minimal. In man, the pulmonary vessels are dilated by histamine, producing a fall in pulmonary artery pressure. The cerebral blood vessels are dilated in majority of the species. In man, administration of histamine produces throbbing headache accompanied by palpable temporal pulsations, and a transient increase in the cerebrospinal fluid pressure. Histamine-induced headache is attributed to stretching of sensory nerve endings around the cranial arteries.

Histamine constricts the large veins. An increase in portal venous pressure after intravenous infusion of histamine has been reported in dogs.

Dilatation of the capillaries and venules accompanied by a fall in blood pressure is a characteristic feature of histamine action in the carnivores (dogs and cats), and in man. This is due to a direct relaxation of the smooth muscle of these blood vessels. Administration of histamine in man produces marked flushing accompanied by a sense of warmth in the face and neck.

Larger doses of histamine also cause an increase in the capillary permeability leading to a

reduction in the plasma volume.

(b) *Blood pressure* : Hypotension, induced by moderate doses of histamine is essentially transient because of rapid destruction of histamine in the body and the presence of protective reflexes. Large doses of histamine, however, may produce prolonged hypotension. This hypotension, if not promptly corrected, eventually leads to irreversible shock and death. Histamine hypotension can be prevented but cannot be adequately reversed by antihistaminic agents. However, it can be reversed by adrenaline injection.

In rabbits and guinea pigs, histamine produces a paradoxical vasopressor effect because of pulmonary and systemic vasoconstriction.

(c) *Triple response* : Intradermal administration of 10 to 20 micrograms of histamine in man produces a characteristic effect described by Lewis as Triple Response. The triple response consists of :

(i) A prompt reddening at the site of injection, with the development of a red spot within a minute, described as 'flush'. The spot then gradually acquires a bluish discolouration. It is attributed to local dilatation of capillaries and venules.

(ii) The flush is followed by the development of a bright 'flare', irregular in outline, extending 1 to 5 cms. beyond the flush. The flare lasts for approximately 10 minutes.

(iii) Development of localized edema, 'wheal', which reaches a maximum within 1½ minutes and is due to escape of fluid from the capillaries.

(d) *Heart* : Histamine increases the sinus rate (Positive chronotropic action); increases the amplitude of ventricular contraction (Positive inotropic action); impairs A-V conduction, increases coronary blood flow and at high concentration induces ventricular arrhythmias such as ventricular fibrillation. In the intact animal, owing to hypotension, there is a reflex increase in the heart rate.

Smooth muscle: Histamine stimulates the smooth muscle of various tissues directly. However, the individual tissue responses show a marked variation. The bronchial and the uterine smooth muscles are highly sensitive to the action

of histamine. Individuals suffering from bronchial asthma and certain other pulmonary diseases develop a sharp fall in vital capacity and considerable respiratory embarrassment in response to histamine. Histamine-induced bronchospasm is effectively antagonised by adrenaline, isoprenaline and aminophylline but not by antihistaminics or atropine.

The gastrointestinal and the ureteral smooth muscles respond moderately to histamine. Histamine, through H_1 -receptors, causes gallbladder contraction while H_2 -receptors mediate gallbladder relaxation.

Exocrine glands : Histamine is a powerful stimulant of hydrochloric acid secretion by the oxyntic cells of the gastric mucosa. This action of histamine occurs with doses lower than those affecting the blood pressure. The gastric secretory response to histamine shows considerable species variation but in man, large doses of histamine augment the secretion of pepsin along with hydrochloric acid.

Secretory response to histamine, though independent of innervation, is reduced after atropinisation or vagotomy. It is blocked by the specific H receptor antagonists.

Central nervous system: Histamine does not cross the blood-brain barrier but is formed locally in the brain from histidine. Like other biogenic amines it activates adenylcyclase in brain leading to accumulation of cyclic AMP. Its central physiological role is not clear.

Miscellaneous actions : Histamine, on introduction into the superficial skin layers, evokes itching and pain. In large doses it produces release of adrenaline from adrenal medulla.

Histamine has an effect on lymphocytes via H receptors and it also inhibits the secretory activity of the mast cells and the basophils which themselves are the source of histamine.

Absorption, fate and excretion : Histamine is a very stable compound and is absorbed from all sites. However, only small quantity of orally administered histamine reaches the circulation because of its metabolism by the intestinal wall and the liver. Histamine metabolism varies

according to the animal species, sex and the organ studied. In man, it is converted into methylhistamine by an enzyme imidazole-n-methyltransferase and then further converted into 1-methylimidazole acetic acid. In some species like rats, it is mainly metabolised by oxidative deamination by the enzyme diamineoxidase, histaminase, present in the liver, kidney and intestinal mucosa.

The enzyme monoamine oxidase also participates in histamine inactivation but its importance in histamine metabolism appears limited.

Adverse reactions : These are due to its pharmacological actions and include hypotension, flushing, headache, visual disturbances, diarrhoea and dyspnoea. Man and guinea pig are extremely sensitive to histamine while rats and mice are highly resistant.

Preparations and dosage : Histamine acid phosphate I.P. injection contains 1 mg. of the drug per ml. Dose : 0.5 to 1 mg. subcutaneously.

Clinical uses : Histamine is mainly used as a diagnostic agent.

To study gastric secretion : Histamine is employed for diagnosis of histamine-fast achlorhydria. In *augmented histamine test*, after determining the basal hydrochloric acid secretion for 30 minutes, an antihistaminic (mepyramine maleate 100 mg. or chlorpheniramine maleate 20 mg.) is injected intramuscularly; this is followed 30 minutes later by a subcutaneous injection of histamine acid phosphate, in a dose of 0.04 mg./kg. of body weight. The antihistaminic pretreatment does not influence the gastric secretion induced by histamine, but effectively blocks its other undesirable effects. The gastric secretory response to histamine is absent in individuals with pernicious anemia. This test is also used to study the acid secretion in patients with peptic ulcer.

Histamine has no valid use in therapeutics.

Histamine substitutes : These are (a) betazole and (b) betahistine hydrochloride.

(a) **BETAZOLE:** This compound, a pyrazole derivative, is 10 times more effective in stimulating gastric acid secretion than histamine but is less active on smooth muscle and blood pressure. In

comparison to histamine, the betazole induced secretory response takes a longer time to develop and has a longer duration. The drug is administered by subcutaneous route in the dose of 0.5 mg./kg. to evoke gastric acid secretion. It can also be administered by mouth. The drug does not require the prior use of an antihistaminic. It should be avoided in patients with allergic disorders.

(b) **BETAHISTINE HYDROCHLORIDE** (Vertin) is a histamine substitute, claimed to reduce the frequency of episodes of vertigo associated with Meniere's syndrome in some patients. The drug causes vasodilatation and improves blood flow to the labyrinth and brainstem. The improvement is symptomatic and short-term. The compound may aggravate peptic ulcer and bronchial asthma.

Histamine liberators : Various agents can release tissue histamine and may thus cause histamine reactions. They are :

(a) *Those which release histamine mainly from the mast cells with minimal tissue damage:*

(i) Proteolytic enzymes like trypsin, certain venoms, food products like crabs, lobsters and fish.

(ii) Surface tension reducing substances like bile salts, anionic and cationic surfactants.

(iii) Substances with a high molecular weight like dextran, and polyvinyl pyrrolidone.

(iv) Certain drugs like d-tubocurarine, morphine, pethidine, stilbamidine, codeine, amphetamine, hydralazine, tolazoline, chlortetracycline and a few antihistaminic drugs.

The most potent histamine-releasing activity is found in chemicals 48/80 and compound 19/35 L. The exact mechanism of histamine release from mast cells by these compounds, however, is not understood.

(b) *Those which release histamine accompanied by tissue damage include:*

(i) Trauma due to cold and chemical, thermal or radiant energy.

(ii) Antigen-antibody reactions.

HISTAMINE, ANAPHYLAXIS AND ALLERGY

The role of histamine in causing anaphylaxis and allergy is discussed in Chapter 1. However, the classical histamine hypothesis does not provide a full explanation of all the effects accompanying anaphylaxis.

In practice, many drugs, sera, chemicals and dietetic articles are capable of causing allergic and/or anaphylactic reactions. Anaphylaxis is a medical emergency and needs immediate treatment.

Treatment of anaphylactic shock :

(a) **Administration of adrenaline :** Adrenaline, on intramuscular administration, produces a dramatic reversal of the hypotension, bronchospasm and laryngeal edema and is life-saving in this condition. The drug may be repeated cautiously after 15 to 20 minutes, if necessary. Intracardiac administration of the drug is rarely indicated and intravenous administration is hazardous owing to the danger of cardiac arrhythmias. For the same reasons it must be used very cautiously in the presence of cardiac irregularities.

(b) **Administration of fluids :** Hypotension associated with anaphylactic shock should be corrected by immediate administration of large quantities of fluids (normal saline and colloids) intravenously. If necessary, norepinephrine can be infused intravenously.

(c) **Corticosteroids :** Corticosteroids are routinely administered in the treatment of anaphylactic shock. Hydrocortisone hemisuccinate 100 mg. is given intravenously, followed later by oral prednisolone. *It must be stressed that corticosteroids are not a substitute for adrenaline which is the drug of choice for this condition.*

(d) **Antihistaminic drugs:** The antihistaminic drugs are not very useful as they are unable to counter the hypotension and bronchospasm characteristic of anaphylactic shock. This may be attributed to involvement of substances other than histamine in the genesis of anaphylactic shock or to release of histamine in intimate contact with

cells not accessible to conventional antihistaminic agents.

Other supportive measures include administration of oxygen and artificial respiration, if necessary.

ANTIHISTAMINIC DRUGS

The actions of histamine in the body can be counteracted by

(a) preventing antigen-antibody reaction that triggers histamine release,

(b) using adrenaline which has actions opposite to those of histamine and thus acts as a physiological antagonist,

(c) hastening the destruction of histamine by using histaminase, which is, however, clinically not effective, and

(d) employing drugs that block the actions of histamine on various receptors. These agents are known as anti-histaminic drugs. They are of two types : *H₁ receptor antagonists* and *H₂ receptor antagonists*.

H₁ -RECEPTOR ANTAGONISTS

In 1933, Fourneau and Bovet showed that certain phenolic ethers possessed antihistamine properties. Since then many H₁ receptor antihistaminic compounds with different chemical structures have been synthesized.

These drugs, synthesized initially to confer protection from the harmful effects of histamine released in the body, fulfil this role only partially. In addition to their antihistaminic activity, many of them also affect the central and the autonomic nervous systems and the contractility of the myocardium.

Experimental methods for studying antihistaminic activity : The anti-histaminic activity can be evaluated either in animals or in humans.

I. Animal methods : Guinea pig, the animal most sensitive to histamine, is commonly employed for evaluation of antihistaminic activity.

The tissues employed for *in vitro* studies are the guinea pig ileum and the tracheal chain. The ability of the drug to inhibit the contractile response of these tissues to histamine is taken as an index of its antihistaminic activity. Alternatively, perfusion of isolated guinea pig lung can be employed for the same purpose.

In intact animals, these drugs are tested for their ability to inhibit histamine induced hypotension in anaesthetized dogs and to protect guinea pigs from lethal effects, produced by either inhalation of 0.2 per cent histamine aerosol or following its intravenous use. They are also evaluated by testing their capacity to prevent flare, whealing and edema, produced by intradermal injection of histamine.

II. Human methods : The human method, employed commonly, measures the protection offered by the agent, administered either by mouth or applied topically, against histamine induced triple response. Histamine reaction is usually produced by intradermal injection of 5 micrograms of histamine acid phosphate on the volar surface of the forearm. Alternatively, histamine can also be administered by anodal iontophoresis.

Classification : The currently available important H₁ receptor antihistaminic agents can be classified either clinically or chemically.

Clinical classification:

I. *Potent and sedative* e.g. diphenhydramine, promethazine and dimenhydrinate.

II. *Potent but less sedative*, e.g. triplennamine, chlorcyclizine and chlorpheniramine.

III. *Less potent and less sedative*, e.g. phenindamine, mepyramine, and pheniramine.

IV. *Newer, non-sedative* e.g. terfenadine, loratadine and astemizole.

Chemical classification : Most of the antihistaminic agents can be represented by the general formula :

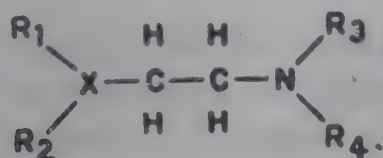


Fig. 20.2 : General structure of antihistaminics.

Depending upon the configuration of X, the anti-histaminic agents can be classified as

I. Ethanolamine derivatives : where $X = O$, e.g. diphenhydramine, dimenhydrinate, doxylamine.

II. Ethylenediamine derivatives : where $X = N$, e.g. tripeleminamine, mepyramine, methapyrilene and antazoline. They have negligible anticholinergic and antiemetic effects.

III. Alkylamine derivatives : where $X = C$, e.g. chlorpheniramine, triprolidine.

IV. Piperazines : where $X =$ carbon in conjunction with a piperazine ring, e.g. chlorcyclizine, meclizine, cinnarizine.

V. Phenothiazines : where $X =$ nitrogen as a part of phenothiazine nucleus, e.g. promethazine, methdilazine, trimeprazine. They have potent antiemetic effect.

VI. Miscellaneous structures : e.g. mebhydrolin, phenindamine.

These antihistaminics cause varying degrees of sedation and except for drugs for group II, they also possess antiemetic effect.

Mechanism of antihistaminic action: Experimental evidence indicates that antihistaminics block histamine actions by competitive antagonism at the receptor sites.

Pharmacological actions of H₁ receptor antagonists :

I. **Antihistaminic effect :** The antihistaminics block histamine effects at a variety of sites. Thus, they antagonize the stimulant action of histamine on the smooth muscle of the gastrointestinal tract, the uterus and the blood vessels and inhibit histamine augmented salivary secretion. In animals, both the hypertensive (in rabbits and guinea pigs) and the hypotensive (cat and dog) responses to histamine are blocked by antihistaminic drugs. They also reduce histamine-induced

triple response and itching but fail to produce resorption of the edema fluid. Antihistaminics prevent the itching, edema, urticaria and increased gastric motility and to a lesser extent, the hypotension produced by the histamine releasing drugs. These agents also antagonize histamine induced bronchospasm in many animal species including guinea pig.

However, the bronchospasm and hypotension developed in man during anaphylactic shock are not adequately countered by them. Likewise, they also fail to inhibit the gastric acid secretion in response to histamine, histamine releasing drugs and anaphylaxis. Further, these agents do not antagonize the cardiac actions of histamine and they control only partially histamine induced flush response in man.

II. **Miscellaneous actions :** These actions are independent of the antihistaminic activity, and vary widely according to the drug used. The important actions are :

(a) *CNS depression* : CNS depression is a common side effect with the majority of antihistaminic drugs in therapeutic doses, and these drugs induce varying degrees of sedation, drowsiness and sleep. Sedation is sometimes beneficial, particularly in the treatment of allergic reactions. The sedative effect often decreases on continued medication. Drugs like promethazine and diphenhydramine are potent sedatives and hypnotics. Sedation is often accompanied by inability to concentrate, dizziness and disturbances of co-ordination, and thus may interfere with daily work.

(b) *CNS stimulation* : Stimulation is less commonly encountered with antihistaminics than depression. Conventional doses of a few drugs such as phenindamine may occasionally produce restlessness, tremors and insomnia and activate latent epilepsy.

(c) *Anti-motion sickness effect* : Motion sickness, attributed commonly to vestibular disturbances, is benefited to a considerable extent by diphenhydramine, dimenhydrinate, promethazine and the piperazine antihistaminics. Vomiting due to other labyrinthine disturbances, such as

labyrinthitis and fenestration operation also responds to antihistaminics. These agents, except the phenothiazine antihistaminics, however, are of limited value in treating emesis due to jaundice, radiation, alkylating agents and pregnancy.

(d) *Antiparkinsonian effect*: See Chapter 19.

(e) *Local anaesthesia* : A large number of antihistaminics exhibit local anaesthetic activity. The basis of this action is probably the marked similarity in the structure of local anaesthetics and the antihistaminic compounds. Promethazine and mepyramine are particularly active as local anaesthetics.

(f) *Autonomic nervous system* : Majority of the antihistaminics exhibit an atropine like activity. Dryness of mouth is a common side effect with antihistaminic therapy. Certain other antihistaminics, such as antazoline and phenindamine, exert an adrenergic blocking effect.

(g) *Cardiovascular system*: Although the therapeutic doses of antihistaminics fail to affect the cardiovascular system, rapid intravenous administration of diphenhydramine, antazoline, methapyrilene, and triplenamine may produce a quinidine-like effect, probably due to their local anaesthetic (membrane stabilizing) action.

Absorption, fate and excretion : The antihistaminic compounds are well absorbed on oral and parenteral administration. Given orally, the antihistaminic effect is manifested within 15 to 30 minutes, reaches the peak by 1 hour and lasts for 3 to 6 hours. The actions of chlorcyclizine and meclizine, however, persist for 8 to 12 hours and 12 to 24 hours respectively. The compounds are mainly metabolized in the liver by hydroxylation and glucuronide conjugation and the degradation products are eliminated in urine.

Adverse reactions : These are as a rule mild. The commonest side effect is sedation and it may be accompanied by fatigue, lassitude, tinnitus, diplopia and euphoria. Individuals taking antihistaminic agents for motion sickness should refrain from driving vehicles because of drowsiness and impairment of co-ordination. Excite-

ment and delirium may rarely occur.

The commonest anticholinergic side effect is dryness of mouth; the others include blurring of vision, tremor, bladder disturbance and rarely impotence. These drugs may occasionally cause nausea, vomiting, epigastric distress, and dysuria. Hypotension and a sense of tightness in the chest may develop rarely.

The antihistaminic agents, in spite of their antiallergic properties, may themselves produce allergic manifestations.

Acute antihistamine poisoning is characterised by marked central stimulation. In children the clinical picture often resembles that of belladonna intoxication, while in adults, fever and flushing are uncommon and drowsiness often precedes the development of delirium and convulsion. Blood pressure and respiration are usually well maintained. Death is due to central depression leading to cardiorespiratory collapse and coma. The treatment is purely symptomatic and supportive. Diazepam may be used to control convulsions.

Preparations and dosage : The number of antihistaminic drugs available in the market far exceeds their utility. The commonly available antihistaminics are mentioned in Table 20.1.

Therapeutic Uses :

(a) *Allergic disorders* : The antihistaminics are beneficial in the suppression of allergic manifestations like polinosis and urticaria. They are extremely effective in the treatment of seasonal hay fever, and considerably reduce the sneezing, rhinorrhoea, and other manifestations associated with this condition. Their efficacy in the treatment of perennial vasomotor rhinitis, however, is much less.

Antihistaminics effectively counter the pruritus and urticaria in atopic and contact dermatitis and that induced by various drugs, chemicals and vegetables, and partially control the pruritus of eczema. Combination of a phenothiazine with an antihistaminic gives better results in severe pruritus than the antihistaminic alone. Systemic administration also controls, to some extent, the pain

and the itch due to bee or wasp stings. The antipruritic action of the antihistaminics is probably nonspecific with regard to their effect on the

mechanism of itch. It is probably related to their central sedative effect. All antihistaminics would appear to be equal in this respect. Their topical

Table 20.1 : H₁ — Receptor Antihistaminic Agents

Name of the compound	Oral Adult Dose	Remarks
Diphenhydramine HCl I.P. (Benadryl)	25 to 50 mg. (parenteral 10 mg)	Moderate antispasmodic and high sedative effect
Dimenhydrinate I.P. (Dramamine, chlorotheophyllinate of diphenhydram- ine)	25 to 100 mg.	Marked sedation. Mainly used for motion sickness
Mepyramine maleate I.P.: (Pyrilamine, Anthisan)	50 to 100 mg. (parenteral 25 to 50 mg.)	Low incidence of sedation
Pheniramine maleate (Avil)	25 to 75 mg.	Moderate sedation
Chlorpheniramine maleate N.F. (Zeet)	5 to 20 mg. (parenteral 5 to 20 mg.)	Slight sedation and high potency
Triprolidine (Actidil)	2.5 to 7.5 mg.	Slight sedation
Cyclizine HCl (Marzine)	50 mg.	Action prolonged. Mainly used for motion sickness
Meclizine HCl (Ancolan)	25 to 50 mg.	Action longer than chlorcyclizine. Mainly used for motion sickness
Buclizine (Longifene)	25 to 75 mg.	Slight sedation. Stimulates appetite
Promethazine HCl I.P. (Phenergan)	12.5 to 25 mg.	Longer duration of action. Marked sedation
Promethazine chlorotheophyllinate (Avomine)	25 to 75 mg.	Used mainly in motion sickness. Superiority over promethazine doubtful
Methdilazine (Dilosyn)	6 to 16 mg.	Slight sedation. Anti-pruritic
Trimeprazine (Vallergan)	2.5 to 5 mg.	Mainly anti-pruritic. Moderate sedation
Antazoline HCl I.P. (Antistine)	50 to 100 mg.	Moderately active; antiarrhythmic
Phenindamine tartrate I.P. (Thephorin)	25 to 50 mg.	May produce central stimulation
Dimethindene (Foristal)	2 to 5 mg.	Anti-pruritic, Slight sedation
Mebrophenhydramine (Mebryl)	25 to 100 mg.	Moderate sedation
Loratadine (Claritine)	10 mg	No sedation
Terfenadine (Seldane)	60 mg b.i.d.	No sedation
Astemizole (Hismanol)	10 mg. once daily	No sedation

use; however, is not recommended owing to the risk of sensitization and a marked tendency to cause eczematous reactions.

Adequate treatment of pruritus depends upon recognition of the local and/or systemic factor(s) responsible for it. For example, adequate treatment of scabies would generally relieve the itching in this condition; the itching in elderly patients, which is due to dryness of the skin, is best treated by moisturising the skin by applying a little edible oil to the affected area immediately after bath and by minimising the use of soap for bathing. Itching due to inflammatory skin conditions can be relieved by a combination of a weak corticosteroid applied locally and a systemically administered antihistaminic. Antihistaminics, however, are ineffective in itching of clinically normal skin.

Reaginic allergy is known to be familial. A period of relative immuno-deficiency may precede frank development of allergic illness in genetically predisposed children. Infants of allergic parents kept on "allergen avoidance regimen" (avoidance of exposure to cow's milk, dairy products, eggs, house dust and pets) for first six months of life had strikingly low incidence of eczema.

Antihistaminics are of some value in controlling mild blood transfusion reactions but not pyrexia or hemolysis. Weak atropine like activity of the antihistaminics and the occasional superimposition of acute cold on chronic allergic rhinitis may account for the beneficial effects of antihistaminic drugs in a few cases of common cold. These drugs, however, are not effective in bronchial asthma and common cold. In fact, some of the antihistaminic agents, by virtue of their atropine-like effect may cause drying of the bronchial secretions resulting in formation of viscid mucus plugs in the respiratory passage and thus, may aggravate already existing bronchial asthma.

Antihistaminics are effective in the treatment of urticaria and angioedema. Urticaria may occur as acute episodes but is considered chronic when it lasts for longer than six weeks. It may occur in a person with atopic history but more often such

history is absent. In a few cases, an allergen (fish, seafood, nuts, eggs; food preservatives and colouring agents like tartrazine; drugs such as aspirin and other NSAID; vegetable gums), a physical offending agent (mechanical trauma, cold, heat), history of insect bites and stings, or underlying disease (infection, connective tissue disorder etc.) may be identified. No such factor is found in majority of chronic urticarias. Mast cells may liberate histamine and other biologically active substances after stimulation by immunological or non-immunological factors, leading to urticaria. A thorough history and a detailed physical examination must precede judicious use of laboratory investigations. If a causative agent can be identified, it must be avoided if it is an external factor and treated if it is a systemic disease. But, a witch-hunt for a 'septic focus' is unrewarding. The treatment of choice for acute urticaria (and acute angioedema) is a subcutaneous injection of adrenaline (1 : 1000 aqueous solution) in the dose of 0.3 ml, repeated if necessary. If adrenaline is contraindicated for some reason, an injection of an antihistamine (50 mg of diphenhydramine I.M. or I.V.) may be used. Antihistamines by mouth are the drugs of choice in chronic urticarias; they are more effective when given regularly on a prophylactic basis than after urticarial lesions start. Sedation is their major adverse effect. The newer, non sedative antihistamines (see below) are effective in chronic urticaria and do not produce sedation. Alternatives to the antihistamines are cyproheptadine, doxepin (an antidepressant with a potent antihistaminic action) or a beta adrenergic agonist such as ephedrine. In resistant cases, an H_2 blocker such as cimetidine or ranitidine may be added to the H_1 blocker. Very few patients need corticosteroids and then, these should be used with circumspection and for the shortest possible period.

(b) Other uses :

(i) The antihistaminics like diphenhydramine and promethazine are often used as hypnotics and rarely as local anaesthetics.

(ii) Promethazine, pethidine and chlorpromazine mixture, termed 'lytic cocktail' has been

employed for production of hypothermia during surgery.

(iii) The antihistaminics, particularly diphenhydramine and orphenadrine, are effective in the treatment of parkinsonism. (See Chapter 19).

(iv) Dimenhydrinate, promethazine and its chlorotheophyllinate (Avomine) and the piperazine antihistaminics are employed in the treatment of motion sickness.

(v) Diphenhydramine 1% and tripeleennamine have been used successfully as local anaesthetic agents in patients in whom 2% procaine cannot be used for some reason. Addition of adrenaline (1 : 50,000) to the above agents for infiltration produces similar effect as on procaine for infiltration.

Since chemically it is fairly easy to modify the basic structure, many compounds having H_1 antihistaminic properties are available for use. The choice of an antihistaminic drug would depend upon its potency, the onset and duration of effective action and the probably undesirable or toxic effects. These vary markedly among different preparations and individuals also vary considerably in their responses to various drugs. None of the preparations available can be considered as ideal for all conditions in all the patients.

Newer, nonsedative antihistaminics : Most of the classical H_1 receptor blocking drugs (antihistaminics) are highly lipid soluble and have marked central nervous system adverse effects including drowsiness. In addition to antihistaminic effect, they also have anticholinergic, anti-serotonergic and anti-bradykin effects. A new class of pure H_1 receptor competitive blockers, which poorly cross the blood brain barriers, is now available. They are the most specific H_1 antagonists available, without any sedative or other central effects. They do not cause sedation in therapeutic doses and are useful in various conditions to the extent that histamine is responsible for the condition. They have a relatively narrow therapeutic range. They are effective in allergic rhinitis but (unlike older antihistamines with multiple actions) not in vasomotor rhinitis. They

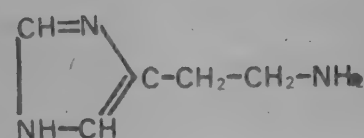
are also useful in urticaria and dermatographia. The two drugs from the group currently available are loratadine (10 mg once a day), terfenadine (dose 60 mg twice a day) and astemizole (dose 10 mg once a day). The former is quick and short acting; the latter is slow and long acting.

HISTAMINE H_2 RECEPTOR ANTAGONISTS

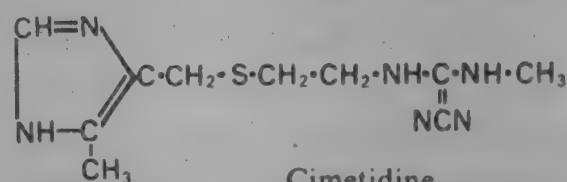
As mentioned earlier, H_2 receptors are responsible for histamine induced gastric acid secretion. H_2 receptor antagonists specifically block this action of histamine by competitive inhibition. These drugs have no direct effect on serum gastrin and gastric emptying is unaffected.

H_2 receptor antagonists block positive chronotropic action of histamine, counter the enhanced automaticity of auricles and ventricles and prevent ventricular-tachyarrhythmias induced by histamine.

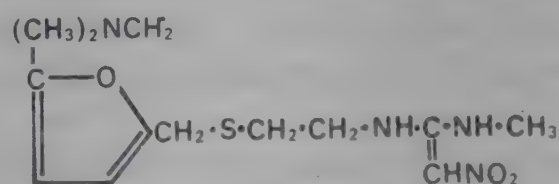
BURIMAMIDE: Burimamide is N-methyl N-(4-(4(5)-imidazolyl) butyl) thiourea. The drug abolishes histamine stimulated gastric acid secretion



Histamine



Cimetidine



Ranitidine

Fig. 20.3: Histamine and H_2 - receptor antagonist

in dogs, cats and rats. It has no atropine like anticholinergic action. Given intravenously, it has been shown to antagonise histamine or pentagastrin stimulated gastric acid secretion in man. It also abolishes the flush induced by histamine infusion in man.

The newer H₂ receptor blocking agents, cimetidine and ranitidine, used in the treatment of peptic ulcer, are discussed in Chapter 38.

H₃ RECEPTORS

There are three types of histamine receptors in the brain H₁, H₂ and H₃. Histamine does not readily cross the blood brain barrier. The histamine receptors mediate the actions of locally synthesized, stored and released histamine. There are two types of histamine containing cells in the brain: histaminergic neurons and mast cells. Histamine is thought to be 'a waking amine' within the

brain and is believed to act by "increasing the sensitivity of large cerebral areas to excitation inputs". It acts through two types of receptor: H₁ receptors which mediate their effects by releasing intracellular Ca⁺⁺ and H₂ receptors which act by releasing intracellular cyclic AMP. Competitive blocking of H₁ receptors by the 'classical' antihistamine drugs and of H₂ receptors by cimetidine leads to drowsiness as an adverse effect. The recently discovered H₃ receptors are thought to be presynaptic autoreceptors that exert a tonic autoinhibitory control on histamine synthesis and release within the brain. Betahistine is a weak, partial agonist at H₁ and H₂ receptors but behaves as a weak H₃ receptor antagonist. It is likely that its activity at H₃ receptors (which allows for facilitated histaminergic transmission) accounts for the improvement in mental functions of elderly patients treated with betahistine.

21 5- Hydroxytryptamine and its Antagonists; Angiotensin, Kinins, Leukotrienes, Cytokines and Prostaglandins

5-HYDROXYTRYPTAMINE (5-HT), also termed serotonin, was isolated in 1948. The same compound, studied independently, termed enteramine by Erspamer and co-workers, was found to have a wide tissue distribution and a variety of pharmacological actions.

Distribution and synthesis : 5-Hydroxytryptamine is widely distributed in plants and in animal tissues, mast cells and platelets. In the mammalian tissues, the highest concentration (60 to 180 micrograms per g.) is present in the pineal gland, where it serves as a precursor for the synthesis of the hormone melatonin. It is also present in the venoms of wasps and bees. Fruits like pineapples, bananas, tomatoes, plums and various nuts contain considerable amounts of 5-hydroxytryptamine.

The compound is synthesized from the amino acid tryptophan. Hydroxylation of tryptophan produces 5-hydroxytryptophan (5-HTP); this reaction is catalyzed by enzyme tryptophan-5-hydroxylase. Decarboxylation of 5-hydroxytryptophan by the enzyme 5-HTP decarboxylase, produces 5-hydroxytryptamine. This enzyme also decarboxylates histidine and DOPA. Within the central nervous system and the gastrointestinal tract, 5-HT is stored in cellular cytoplasmic granules similar to the chromaffin granules that store catecholamines.

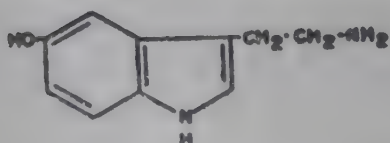


Fig 21.1 : 5-Hydroxytryptamine

There is now strong evidence that 5-HT receptors are of three types- 5HT₁, 5HT₂ and 5HT₃ with further subdivision of 5HT₁.

Pharmacological actions:

I. Cardiovascular system : (a) *Peripheral blood vessels:* 5-HT is a constrictor of majority of blood vessels including the renal, meningeal and pulmonary arteries. In several species, the cerebral blood vessels are constricted powerfully. It also narrows the veins and venules, but dilates the blood vessels of skeletal muscles, the coronaries and the capillaries of the skin. Administration of 5-HT in humans results in cutaneous vasodilatation, producing initially a bright red flush, that may be converted to cyanosis, probably owing to peripheral pooling of blood. In rodents, capillary dilatation induced by 5-HT is accompanied by an increase in their permeability.

(b) *Heart :* 5-HT has weak direct positive inotropic and chronotropic effects on the myocardium; these, however, are usually not demonstrable in human beings, as it also causes reflex bradycardia.

(c) *Blood pressure :* A characteristic 'triphasic response' is observed after intravenous injection of 5-HT in majority of the animal species including man. It consists of an initial transient depression attributed to increased vagal activity following stimulation of coronary and carotid chemoreceptors, followed by an immediate rise in blood pressure, due to peripheral vasoconstriction; later on, it causes a sustained hypotension which is due to dilatation of skeletal muscle blood vessels.

II. Smooth muscle : 5-HT stimulates smooth muscles, the most significant effect being seen on the small intestine. Both the tone and the motility are initially augmented followed by an inhibition

of the spontaneous activity. The compound also evokes bronchoconstriction in many animal species.

III. Central nervous system : Considerable quantities of 5-HT are found in the midbrain, the limbic system, the hypothalamus, the caudate nucleus and the pituitary gland. 5-Hydroxytryptamine, administered exogenously, does not readily cross the blood-brain barrier. The barrier, however, does not exist for its precursor, 5-HTP. Intraventricular administration of the compound in an unanaesthetized cat evokes tremors and muscular weakness, accompanied sometimes by profuse salivation. The cat becomes catatonic but not sleepy.

IV. Miscellaneous actions :

(i) 5-HT has been demonstrated to facilitate ganglionic transmission and produce release of adrenaline from the adrenal medulla.

(ii) It reduces the volume, acidity, and pepsin content of the gastric juice and promotes the production of mucus.

Absorption, fate and excretion : 5-HT, on oral administration, is not significantly absorbed as it is degraded rapidly within the gastrointestinal tract. It is satisfactorily absorbed on parenteral administration. Although platelets cannot synthesize 5-HT, they do have the capacity for its uptake and storage. It is mainly metabolized by the enzyme monoamine oxidase (MAO) and excreted as 5-hydroxy indoleacetic acid (5-HIAA) in the urine. The upper limit of normal urinary 5-HIAA in man is about 10 mg per day.

Significance of 5-hydroxytryptamine: The exact physiological role of 5-hydroxytryptamine is not known.

(a) **Neurohumoral transmission :** 5-HT is present in the nervous system of all the vertebrates and many invertebrates. Considerable evidence indicates that 5-HT is indeed a chemical transmitter released by 'tryptaminergic' neurones widely distributed in the brain. One of the important functions attributed to the tryptaminergic raphe neurones is dampening of over-reactiveness to various stimuli and altered tryptaminergic function may be responsible for disturbances in sleep,

mood, sexual behaviour, motor activity and perception. These neurones are also involved in other functions such as temperature regulation, endocrine control and extra-pyramidal activity. Evidence favouring the role of 5-HT neurones in initiating or maintaining non-REM sleep is controversial. 5-HT is, however, involved in some way in regulation of the state of consciousness. Many centrally acting drugs are known to influence responses to 5-HT or alter its uptake, synthesis, storage, release or catabolism. Prominent among these are anti-psychotic drugs like chlorpromazine, reserpine, antidepressants, hallucinogens like LSD, mescaline and even analgesics like morphine.

(b) **Psychiatry :** Disturbances in the brain 5-HT metabolism are suspected as a cause of certain psychiatric disorders such as schizophrenia and affective disorders. 5-HT₂ receptors present in brain in limbic and cortical areas are known to be involved in controlling mood, emotion, reward and memory. 5-HT₂ receptor antagonists reduce the increased psychomotor drive associated with a mesolimbic dopamine excess. Such antagonist improves impaired cognitive performance in animals.

Anti-emetic activity has generally been associated with dopamine antagonist drugs such as metoclopramide but recent studies in animals indicate that selective 5-HT₂ receptor antagonists can prevent emesis associated with anti-cancer drugs and radiotherapy. 5-HT₂ receptors are present in high densities on afferent vagus nerves and in the area postrema and dorsal vagal complex of animals.

Role of 5-HT in migraine has been suspected for long time; headaches are triggered in susceptible individuals by 5-HT releasing agents. It now seems that specific 5-HT₁ like receptors occur predominantly in certain cranial blood vessels supplied by the carotid arteries. Stimulation of these receptors causes constriction of the arterio-venous shunt vessels to redirect the blood flow to the capillary bed. Ergotamine appears to relieve migraine by such mechanism.

(c) **Gastrointestinal tract :** Because of the

high concentration of 5-HT and 5-HTP in the gastrointestinal mucosa, 5-HT is claimed to act as a local hormone for the initiation and sustenance of intestinal peristalsis.

(d) **Hormone secretion** : There is some evidence to suggest that tryptaminergic mechanisms are involved in the control of release of certain hormones. (See Chap. 58)

(e) **Carcinoid syndrome** : This is a clinical syndrome known to be associated with argentaffin cell tumours of the gastrointestinal tract which secrete 5-HT. These tumours are locally invasive and may occasionally metastasize. Carcinoid syndrome is characterised by intermittent attacks of flushing, hypotension, bronchospasm, colic and diarrhoea. A picture of tricuspid incompetence and pulmonary stenosis is occasionally observed. Some of these manifestations are believed to be due to excessive production of 5-HT. The diagnosis is usually confirmed by demonstrating high plasma 5-HT and high urinary H.I.A.A. levels. It should be noted that a moderate increase in urinary H.I.A.A. levels can occur in patients with malabsorption states such as sprue and the blind loop syndrome. The drug parachlorophenylalanine (PCPA, Fenclonin) inhibits 5-HT synthesis by inhibiting tryptophan hydroxylase. PCPA in a daily dose of 2 g. results in almost complete inhibition of this enzyme leading to stoppage of diarrhoea, cramps and decrease in 5-HIAA excretion in urine. However, flushing is not much affected. The toxicity of PCPA includes allergic reactions, tinnitus, fatigue, dizziness and mental changes. Marked hypothermia following PCPA administration in man has been reported.

(f) **Miscellaneous** : 5-HT is believed to be responsible for the edema, flare, pain and itching produced during inflammation. It appears that 5-HT is a mediator of acute inflammation only in rats and mice. The human skin, however, does not contain significant amounts of 5-HT and the 5-HT antagonists are not effective in controlling inflammation in human beings.

5-Hydroxytryptamine Antagonists : Apart from PCPA, 5-HT synthesis can be inhibited by α methyl dopa, some halogenated trypto-

phans, and phenylalanine.

A number of compounds antagonize the actions of 5-HT on the tissues. These include lysergic acid diethylamide (LSD) and its derivative 2-brom LSD or BOL. The latter is not hallucinogenic but effectively antagonizes the actions of 5-HT on smooth muscles. Other compounds like phenoxybenzamine, chlorpromazine and yohimbine also block the actions of 5-HT. Since there are multiple types of 5-HT receptors, a drug acting as antagonist at one site may not act similarly at others. The 5-HT antagonists of therapeutic importance are ;

(a) **METHYSERGIDE** : Methysergide a congener of LSD, blocks the actions of 5-HT on a variety of smooth muscles and has independent feeble vasoconstrictor and oxytocic effects. The drug is a potent peripheral 5-HT antagonist and acts centrally as a 5-HT agonist.

Methysergide is an effective prophylactic agent in the management of migrainous headaches. The protective effect of the drug develops within 24 to 48 hours after initiation of therapy and persists for a similar period after its withdrawal. Rebound headaches may occur after sudden cessation of therapy.

It is indicated for use in patients whose migrainous headaches are sufficiently frequent and severe to warrant continuous therapy. It is of no value in treating an acute attack and, in fact, may exacerbate such a condition. Its exact mechanism of action in the prevention of migrainous headache is not known.

It is administered orally, initially in the dose of 1-2 mg. 2-3 times daily with meals. Continuous therapy with methysergide should not be given for more than 6 months without imposing a drug free period of 3 to 4 weeks. The dosage should be gradually reduced over 2 to 3 weeks before discontinuing the drug. For other drugs used in migraine see Chapter 40.

Adverse reactions : These include gastrointestinal irritation, drowsiness, vertigo and psychic disturbances. Postural hypotension, tachycardia, restlessness, insomnia, edema, neutropenia and

paraesthesiae, have been reported. A mild to severe peripheral arterial insufficiency, precipitation of angina, aggravation of peptic ulcer, retroperitoneal fibrosis with obstruction of the urinary tract and pleuro-pulmonary fibrosis are other, rare but serious, toxic effects. The drug should be avoided in patients with pregnancy, severe hypertension, peripheral vascular disease, peptic ulcer, renal disease and coronary insufficiency.

(b) **CYPROHEPTADINE (Periactin)** : This compound, which bears some structural resemblance to phenothiazines, is a potent antagonist of 5-HT and to a smaller extent of histamine and acetylcholine. Large doses administered to animals produce central depression. The drug also has anticonvulsant, and antitremor activities. Cyproheptadine is satisfactorily absorbed from the gastrointestinal tract. The metabolic fate of the compound is not known.

It stimulates appetite probably by acting directly on the hypothalamus. Weight is gained rapidly during the first few weeks of therapy and is lost again when the drug is stopped. There is evidence that 5-HT is involved in the control of ACTH secretion, possibly by stimulating corticotrophin releasing factor (CRF) secretion from the hypothalamus. Administration of cyproheptadine can block the release of hydrocortisone and has, in fact, been used in the treatment of ACTH dependent Cushing's disease. It has also been shown to suppress aldosterone production in idiopathic aldosteronism.

Adverse reactions : The common adverse effect is drowsiness. It is, however, transient and seldom necessitates withdrawal of the drug. Other adverse reactions, reported occasionally, include dryness of mouth, mental confusion, ataxia, dizziness, headache and visual hallucinations.

Therapeutic uses : Cyproheptadine is mainly useful in relieving pruritus associated with such skin disorders as allergic dermatitis, urticaria and neurodermatoses. The therapeutic efficacy of the drug in pruritus is probably due to its antihistaminic effect as the human skin does not contain significant amounts of 5-HT. The 5-HT antago-

nizing properties may be useful in the treatment of postgastrectomy dumping syndrome and in carcinoid syndrome.

Cyproheptadine may also be useful in providing symptomatic relief of seasonal and perennial pollinosis. The drug, however, is of little value in the treatment of bronchial asthma.

Although it has been used as appetite stimulant in certain diseases, its promotion as a general appetite stimulant or tonic is not justifiable and even dangerous.

Cyproheptadine is administered by mouth in the dose of 4 to 20 mg. per day in divided doses.

(c) **KETANSERIN** : 5HT (serotonin) binds to two receptor sites S_1 and S_2 . Ketanserin selectively blocks the S_2 receptor and thereby antagonises vasoconstriction, platelets aggregation and bronchoconstriction. The drug has been used to improve digital circulation in patients with traumatic vasospastic disease.

ANGIOTENSIN : The synthesis of angiotensin and its role in the genesis of essential hypertension are discussed in Chapter 26. The important pharmacological actions of ANGIOTENSIN AMIDE (Hypertensin), a synthetic substance, which is chemically a minor structural variant of the naturally occurring angiotensin II, are described below.

Pharmacological actions : Angiotensin amide is a powerful vasoconstrictor agent. The pressor effect is due to direct stimulation of the smooth muscle of blood vessels with the attendant increase in the total peripheral resistance. The precapillary blood vessels are constricted much more than the postcapillary vessels and veins. The cutaneous, splanchnic and renal blood vessels are strongly constricted with a resultant decrease in the blood flow; the cerebral, coronary and skeletal muscle blood vessels are only weakly constricted and the blood flow in these regions increased following the rise in blood pressure; the effect on the pulmonary vessels is negligible. Cardiac muscle is not stimulated.

Recent evidence indicates that angiotensin II may play an important role in the central control

of the cardiovascular system. It has been shown to act on C.N.S. sites to increase arterial blood pressure, increase A.D.H. secretion and stimulate thirst.

Clinical observations indicate that angiotensin amide is 2 to 3 times more potent than noradrenaline in its pressor activity. It is devoid of tachyphylaxis. It produces a prompt initial decrease in the quantity and electrolyte content of urine followed by diuresis (owing to inhibition of sodium reabsorption by distal tubule) in normotensive individuals, but in certain hypertensive individuals and in those with cirrhosis and ascites, it causes a brisk diuresis. The explanation of this phenomenon is not available.

Angiotensin amide probably has lower tendency to cause cardiac arrhythmias than noradrenaline. However, serious ventricular irregularities can occur. Frequent recording of blood pressure is essential during its administration. It is important to note that hypotension refractory to noradrenaline may respond to angiotensin amide and vice versa. The drug can cause dizziness, headache, and bradycardia. However, unlike noradrenaline, spasm of the infused vein and tissue necrosis do not occur.

It is supplied in vials containing 2.5 mg. of the lyophilized powder, to which 5 ml. of sterile distilled water is added before use. The required amount of this solution is infused intravenously in 500 ml. of glucose saline. The effective rate of infusion varies from 0.5 to 20 micrograms of the drug per minute. (See also Chapt. 26).

KININS : The kinins are polypeptides released from an α_2 globulin fraction of the plasma, termed *kallidinogen* or *bradykininogen*, by the action of enzymes termed *kallikreins*. The kallikreins (Kallikreas, the Greek name for pancreas) are present in human plasma, pancreatic and salivary secretions, other biological fluids and urine; normally no kinin formation takes place as these enzymes are present in inactive forms called *kallikreinogens*. The activation of kallikreinogens to kallikreins is achieved by contact of

plasma and other fluids with a foreign surface, change in plasma pH or its dilution with saline.

The important kinins are the decapeptide (containing 10 amino acid residues) kallidin and the nonapeptide bradykinin and are referred to as the 'plasma kinins'.

In addition to kallikreins, various other agents such as proteolytic enzyme trypsin and certain snake venoms are capable of converting kallidinogen to kallidin. Preformed kinins exist in the venoms of wasps and hornets.

The kinins are the most powerful vasodilating agents and have about 10 times the vasodilator activity of histamine and produce a spectacular flushing of the face, neck and upper part of the body, on intravenous administration in humans. The major blood vessels are dilated. The kinins also have direct positive chronotropic and inotropic actions on the myocardium and in moderate doses, release adrenaline from the adrenal medulla.

The kinins stimulate other smooth muscles including those of the uterus, the bronchi and the gastrointestinal tract. The term bradykinin was coined initially to signify the slow contraction of the gastrointestinal smooth muscle in response to the nonapeptide. The bronchoconstrictor effect of the kinins is selectively antagonized in guinea pigs by salicylates. They, however, do not inhibit the vascular effects of the kinins.

The kinins evoke pain and itching on application to the base of a blister. Intradermal injection of kinins produces a wheal accompanied by flare owing to vasodilatation and a marked increase in the capillary permeability. NSAID can antagonise the pain producing property of kinins. Salicylates and glucocorticoids have been reported to inhibit kallikreinogen activation.

The kinins are rapidly inactivated by the plasma and erythrocyte amino-peptidases and carboxypeptidases.

Physiological role : The kinins, because of their extreme potency, have provoked a great deal of speculation regarding their functions. They have been incriminated in the processes of inflam-

matory and anaphylactic reactions and in shock. They may also modulate migration of WBC and tissue cells that take part in the inflammatory process. They are also most potent activator of PG-release, including PGI_2 from vessels. A high molecular weight polypeptide (Trasylol), extracted from the parotid glands and lymph nodes of cattle, which inhibits and inactivates kallikrein, trypsin and other proteolytic enzymes, has been used in the treatment of acute pancreatitis and other diseases with increased proteolytic activity with equivocal results.

LEUKOTRIENES : Leukotrienes (LTs) are formed from arachidonic acid by the action of 5-lipo-oxygenase. (Fig. 21.2) Five LTs, namely LTA_4 , LTB_4 , LTC_4 , LTD_4 , LTE_4 have been identified and characterized. Of these, last three are also known as slow-reacting substances (SRSs).

LTs probably act as 'local hormones' and their half-life in blood is very short. They are released by various immunological and non-immunological stimuli from a number of tissues including human lung and white blood cells. The enzyme 5-

lipo-oxygenase is present in various body fluids and also found in venoms of snakes and bees.

The LTs have potent biological actions. LTB_4 produces chemotactic, chemokinetic and aggregatory actions on polymorphs, causes exudation of plasma in the skin and contraction of guinea-pig and human lung strips. It is released during anaphylaxis along with LTD_4 . Slow reacting substances (LTC_4 , LTD_4 , LTE_4) have similar actions. SRS-A is now identified as LTD_4 . SRSs cause bronchoconstriction by direct action. They also produce exudation of plasma in skin and constriction of blood vessels including coronary vessels, resulting into reduction in coronary flow. SRSs are probably responsible for narrowing of the airways, increased mucous secretion and oedema of the bronchial mucosa observed in asthma and during anaphylaxis. All LTs may play important role in inflammation.

CYTOKINES: Inflammation is one of the integral parts of the body defence mechanisms and several polypeptides are claimed to mediate some aspects or other of the inflammatory process. One of the groups of polypeptide mediators released from a variety of cell types, not just lymphocytes,

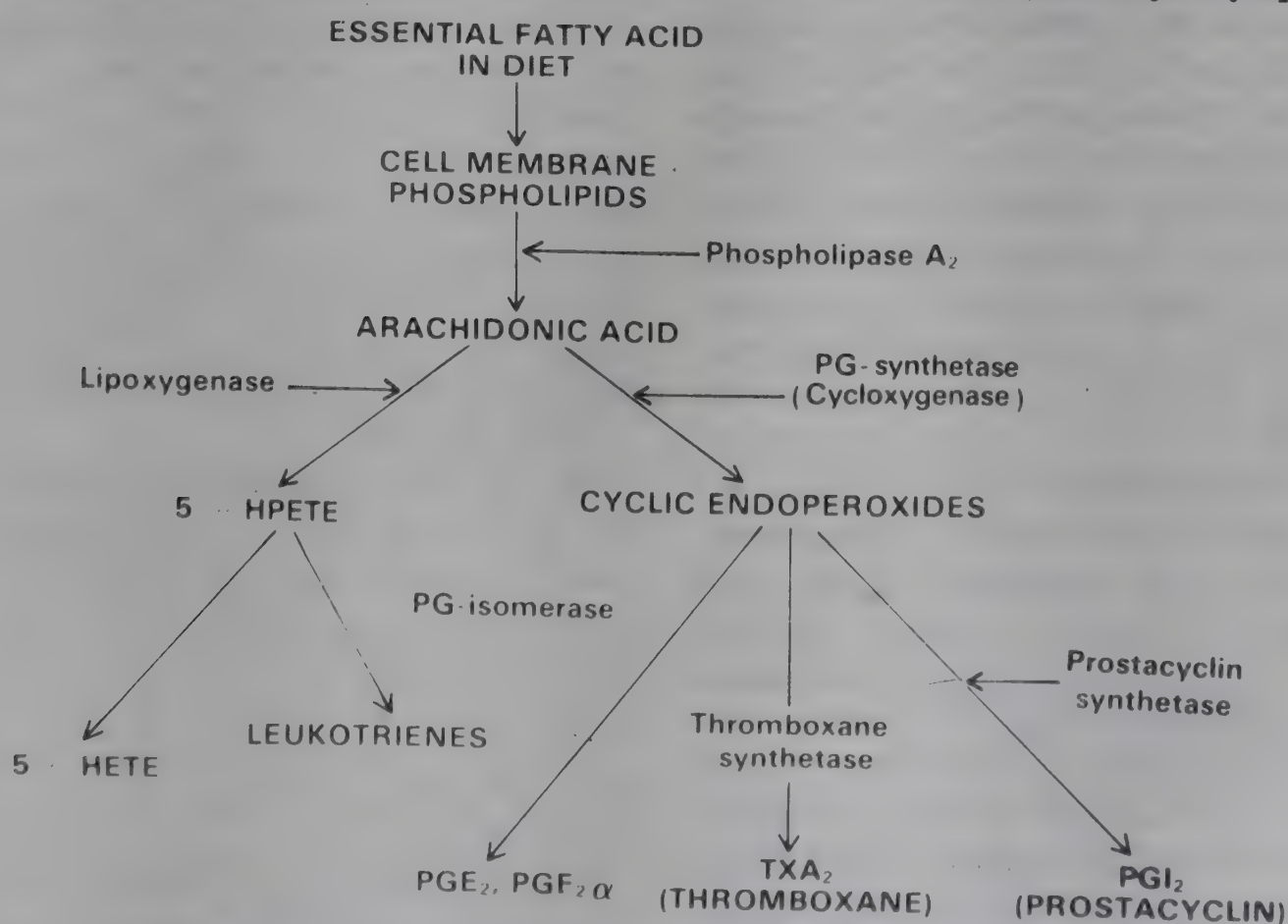


Fig. 21.2 : Synthesis of important mammalian prostaglandins (PG)

which activate, modulate and control various aspects of body defence and repair are termed as *cytokines* or *lymphokines*. The coordination of the body defence mechanisms appears to involve the synthesis and release of a few key cytokines of which **Interleukin-1 (IL-1)** and **tumour necrosis factor (TNF, cachectin, lymphotoxin)** are considered to play an important role in the overall inflammatory process, and in immunity and tumour killing mechanisms. **Interleukin-2 (IL-2)** is produced from T-cells and is a growth factor for other lymphocytes, while **Interleukin-3 (IL-3)** is one of the colony stimulating factors.

IL-1 activity can be produced by virtually all nucleated cell types - like macrophages/monocytes, lymphocytes, neutrophils, fibroblasts, osteoblasts etc. Various stimuli such as bacterial products, lymphocyte products and a gamut of noxious stimuli that can cause tissue damage, as well as TNF, cause IL-1 production and release. In contrast, TNF/cachectin appears to be produced by only monocytes and macrophages and lymphotoxin by lymphocytes.

IL-1 and TNF have many similarities in regard to physical and biochemical properties, synthesis and release, and they possess overlapping biological properties and functions. The target cells and responses to cytokines fall broadly into two categories of function (i) *the defence role* of alerting the body to invasion and dealing with it, and (ii) *the repair role* of cleaning up the debris and replacing lost matrix and tissue. IL-1 also produces metabolic responses; thereby, the necessary energy resources and rebuilding materials are mobilized.

Role in body defence:

IL-1 causes erythema, edema, chemo-attraction, adherence and migration of defence cells into the sites of inflammation. Both IL-1 and TNF can induce the burst in neutrophils and monocytes and the associated production of radicals myeloperoxide and hydrogen peroxide, that play an important role in killing the invading organisms. The cytokines activate the cells leading to release of hydrolytic enzymes and to increase in prostaglandins (PG) production. Inhibition and

killing of tumour cells is yet another property of TNF and to a lesser extent of IL-1. These cytokines inhibit the replication of certain RNA and DNA viruses and induce viral resistance in a variety of cell types; this is not due to induction of interferons. Thus, many of the events associated with the acute inflammatory reaction and defence against infections of various kinds can be mediated by IL-1 and TNF. In addition, IL-1 plays an important role in the proliferation of various classes of lymphocytes responsible for the immune component of inflammatory diseases; TNF in contrast to IL-1 has little influence on lymphocyte proliferation and immune responses.

Role in body repair :

Both IL-1 and TNF appear to have considerable influence on the earlier repair events of debridement, mitogenesis and differentiation. Release of enzymes including proteoglycanase, collagenase, and gelatinase can be induced from fibroblasts, synoviocytes and chondrocytes by IL-1 and the same is true for TNF. Enzyme release is accompanied by release of PGE_2 , which may also contribute to the degradation process. Local release of IL-1 and TNF could thus mediate debridement; it is also possible that their inappropriate release could mediate the matrix destruction observed in rheumatoid arthritis. TNF and IL-1 both can induce bone resorption. Overall, IL-1 and TNF possess the potential for mediating many of the events crucial to defence of the host, and subsequent repair but by the same token they may also mediate much of the tissue destruction which characterizes the connective tissue diseases.

Metabolic role:

IL-1 and TNF are both potent pyrogens, exerting their effect directly at the hypothalamus; raised body temperature facilitates killing of infecting organisms. It is possible that the body wasting and cachexia seen with severe disease states is due to the catabolic properties of TNF.

Cytokines act on hepatocytes and cause increase synthesis of acute phase plasma proteins (APP). TNF and PGE_2 can also cause a rise in APP by different mechanisms. The severity, progression and outcome of connective tissue dis-

eases, for example the erosive progression of rheumatoid arthritis, and number of ischemic heart events during atherosclerosis correlate with APP levels as well as the effect of therapy.

The inflammatory cytokine release and activity are highly controlled, probably by several mechanisms, still not understood.

PROSTAGLANDINS (PGs) : In 1930, Kurzrok and Lieb demonstrated the activity of human semen on isolated strips of human uterine muscle. This was confirmed by von Euler (1935) who demonstrated a substance present in the extracts of human seminal fluid, which caused contraction of the isolated intestine and the uterine muscle, and vasodilatation. This substance was named as prostaglandin because of its probable origin from the prostatic gland. Bergstrom and associates have now shown that the various PGs are closely related derivatives of the lipid soluble prostanoid acid. Although human seminal fluid is the richest known source, PGs are also present in various other tissue extracts such as those of iris, lung, human menstrual fluid, brain, thymus, pancreas and kidneys. Prostaglandin of the human semen is a mixture of six closely related substances belonging to the groups E, F, A and B. The other human tissues contain mostly groups E and F prostaglandins though PGD₂, PGG₂, PGH₂ and PGI₂ (Prostacyclin) have also been described. The corals, native to the Caribbean sea contain large quantities of PGA as a natural constituent.

The PGs are biosynthesized from polyunsaturated fatty acids belonging either to the linoleic or the α -linolenic series. The former series is the source of the two principal mammalian prostaglandins, PGE₂ and PGE₂ α . The PGs A, B and C arise from PGE₂ by dehydration and isomerization. Most tissue cells are capable of synthesizing PGs from the dietary essential fatty acids. These substances are released into the body by a host of mechanical, thermal, chemical and bacterial insults. Both PGE₂ and PGI₂ are potent vasodilators and hyperalgesic agents. PGE₂ is also a potent pyrogenic substance. In association with

other mediators they play an important role in the development of inflammatory response.

All PGs contain one or more double bonds, the number of which is indicated by suffixing the number such as PGE₂.

Physiologically, PGs are synthesized at the site of action. They are very active even in low concentrations and are destroyed quickly. Because of their instability, short duration of action and lack of tissue specificity, the natural PGs themselves have limited clinical applications. Various synthetic derivatives, however, are now being investigated to overcome these difficulties.

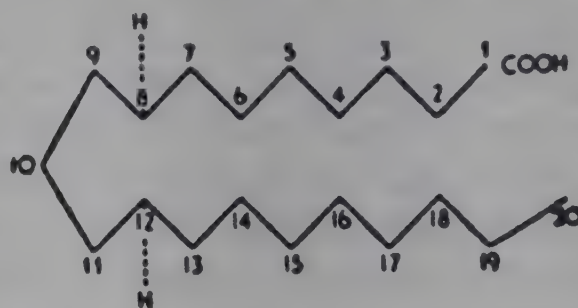


Fig. 21.3 : Chemical structure of prostaglandins.

Pharmacological actions : (a) *Smooth muscles* : Majority of the PGs stimulate the human myometrium and increase the intestinal motility. The actions of PGE and PGF₂ α on the uterine muscle are discussed in Chapter 40. PGE inhibits the tone of tracheal and bronchial muscles and thus has a bronchodilator action.

(b) *Gastrointestinal system* : Prostaglandins are distributed throughout the gut though their concentration varies in different parts of the gut. PGE₂ inhibits the gastric acid secretion and has a cytoprotective effect on gastric and duodenal mucosa in humans. Both PGE and PGF cause contraction of the longitudinal muscle of the gut. Further, PGs stimulate intestinal fluid secretion and cause diarrhoea when administered orally or parenterally in man. These findings suggest a possible role of PG release in certain types of diarrhoeas. Aspirin or indomethacin can counter PG effects on the intestine (See Chapters 37 and 39).

(c) *Cardiovascular system* : PGE₂ and PGA₂ produce peripheral vasodilatation and can

lower the blood pressure. They are powerful natriuretic agents. PGF, however, constricts arterioles and veins. They may also increase the heart rate and the force of cardiac contraction.

PGE₁ is a potent relaxant of the smooth muscle of the ductus arteriosus and preserves the ductal patency in the newborn; this action has found therapeutic application.

(d) *Reproductive system* : Apart from their stimulant action on the uterine smooth muscle, PGs have been shown to exert various other actions on the reproductive system. It has been observed in animal experiments that PGs cause regression of the corpus luteum (Luteolysis) and reduction in secretion of progesterone. This can prevent the implantation of fertilized ovum. Phenoxy-prostaglandin which has a marked luteolytic potency is being tried in veterinary practice to produce luteolysis and for induction of oestrus and ovulation on demand.

(e) *C.N.S.* : Prostaglandins have been shown to produce many actions on the central nervous system and the role of prostaglandin as a transmitter substance has been suggested.

(f) *Platelet aggregation* : It is likely that PGs play a physiological role in platelet function. PG endoperoxide, thromboxane A₂ (TXA₂), causes platelet aggregation and vasoconstriction, while PGI₂ (Prostacyclin) which is found in the vascular endothelium is a potent inhibitor of platelet aggregation and causes vasodilatation. It has been suggested that when the platelets are damaged they release PG endoperoxides which cause aggregation of platelets. However, the vascular endothelium generates PGI₂ which has anti-aggregatory effect. Damage to the endothelium reduces PGI₂ synthesis and increases the tendency for blood to clot because of the unopposed action of TXA₂. Aspirin blocks formation of both TXA₂ and PGI₂. (See Chapt. 29).

(g) *Miscellaneous* : PGE₁ and PGE₂ block the lipolytic effect of adrenaline, ACTH and glucagon. They also produce pain when applied to an exposed blister base. Presence of PGE and kinins in the inflammatory exudates suggests a

possible role of these substances in the genesis of inflammation. Aspirin and indomethacin are potent inhibitors of the synthesis of prostaglandins.

Some PGs are potent bone resorbing agents which act by stimulating osteoclasts. Experimentally, bone destruction induced by implanted metastasizing tumours in rats and rabbits, can be reduced by aspirin or indomethacin.

Platelet activating factor (PAF -acether) : This an ether linked phospholipid, is shown to possess a wide range of biological activities. It is released during mast cell degranulation and is implicated in pathophysiological states including allergic inflammation, anaphylactic shock and bronchial asthma. It is also formed by eosinophils, macrophages, neutrophils and vascular endothelium. It activates most inflammatory cells and is believed to be responsible for mobilisation of eosinophils and/or platelets in lungs after exposure to the allergen. Intradermal injection of PAF in man causes a biphasic inflammatory response in the skin, with acute and late onset components similar to the response to moderate doses of allergens in sensitized individuals. Given by aerosol inhalation, it causes dose dependent broncho-constriction and inflammation of airways. The microvascular permeability is increased, leading to edema of the airways. Further, it also induces non-specific bronchial hyper-responsiveness in guinea pigs and in non-asthmatic human subjects.

Recently, a substance called *Ginkgolides* has been isolated from the extracts of the tree *Ginkgo biloba* used in China for the treatment of asthma. The active ingredient has been found to exert specific PAF receptor antagonistic activity. Thus, it causes inhibition of PAF induced platelet aggregation, of degranulation of isolated, human neutrophils, and of oxygen radical production by the human neutrophils. Its possible use in the treatment of bronchial asthma and other allergic disorders is under investigation.

Section VI : Drugs Used in Respiratory Disorders

22 Pharmacotherapy of Cough

Cough is a protective reflex which helps to expel irritant matter from the respiratory tract. This is necessary for preventing mechanical obstruction to breathing. Cough reflex is basically a variant of the respiratory reflex and is present even in animals like cat and dog. Irritation of the respiratory tract at various sites such as pharynx, larynx, trachea or bronchi produces tussal impulses which are carried by afferent fibres in the vagus and sympathetic nerves to the cough centre located in the medulla oblongata, which initiates the act of coughing. Some workers believe that such irritation first produces bronchospasm which then initiates cough reflex by stimulating cough receptors which are probably a specialized type of stretch receptors located in the tracheobronchial tree.

The act of coughing involves an initial deep inspiration followed by forced expiration against a temporarily closed glottis. Closure of the glottis causes an increase in intrathoracic pressure. When the glottis opens suddenly, the pulmonary air is forced through the trachea almost at the speed of sound. As a result of this, the respiratory tract secretions are thrown out as expectoration. The cough reflex has a tremendous reserve capacity and most coughs are greatly in excess of that required to expel particulate material. Furthermore, the strong expiration leads to a stronger succeeding inspiration and thus produces a vicious cycle in the form of a fit of coughing. Cough may be *productive*, associated with a large amount of sputum, or *dry* and without much sputum.

Environmental irritants may cause cough by irritating the lungs, trachea or bronchi. Smoking cigarettes is a well known cause of chronic persis-

tent cough. Cough due to the inhalation of allergens such as dust, chemicals and pollen is commonly observed in asthmatics. The commonest cause of transient cough is the common cold. This cough is somewhat noisy and worsens at night and is most commonly caused by postnasal drip of mucus that stimulates receptors in the pharynx. A similar mechanism probably operates in case of chronic persistent cough observed in persons with allergic rhinitis, chronic sinusitis and obstruction due to enlarged adenoids. Enlarged, infected tonsils, and abnormally elongated uvula or nasal polyps can also cause chronic persistent cough.

Important causes of cough include:

(i) Upper respiratory tract infections, which are usually mild and self-limiting.

(ii) Acute lung infections, asthma, and pleural diseases where therapy of the underlying cause will relieve cough, and

(iii) Chronic pulmonary diseases like chronic bronchitis, bronchiectasis, tuberculosis and lung cancer where symptomatic treatment for cough is essential along with the specific therapy.

(iv) Secondary to acute left ventricular failure, which calls for immediate attention to the cardiac condition.

Outside the respiratory tract, disorders of the external auditory canal and ear drum, pericardium and even of stomach can give rise to chronic non-productive cough. Thus, wax impacted in the ear, inflammation or eczema or even irritation of the drum by hair have all been known to cause cough. The entity called 'psychogenic cough' is well known; it is non-productive and not present during sleep, usually becoming worse with emotional stress.

Definitive treatment of cough depends upon its

cause. Thus, stoppage of smoking would correct chronic cough in heavy smokers. The cough caused by a hair irritating the ear drum would dramatically disappear with removal of hair, while the cough caused by post-nasal drip due to allergic rhinitis would be benefited by antihistaminic therapy. Mild cough needs hardly any active therapy. Only when cough serves no useful purpose and may in fact cause complications, symptomatic treatment is indicated.

In case of productive cough, the patient should be encouraged to cough voluntarily in appropriate posture from time to time. In cases of bronchiectasis or lung abscess, postural drainage aided by percussion of the chest is very useful. Since inflamed trachea or bronchi can get irritated by cold or dry air, a warm room with humid atmosphere is beneficial, particularly during the cold season when the natural respiratory tract fluid is reduced in quantity. Many patients with cough feel comfortable after a cup of hot tea or even hot water; and simple steam inhalation has a beneficial effect in liquefying tenacious respiratory tract secretions.

Drugs which are used in the symptomatic treatment of cough are called as **antitussives** (tussis : Latin for 'cough'). These drugs are used for immediate symptomatic relief of cough and do not serve as substitutes for the specific therapy of the underlying pathological condition. Antitussives can be classified as :

(a) Those acting as pharyngeal demulcents and local sialogogues, e.g. syrups and linctuses.

(b) Those which increase the respiratory tract fluid, e.g. expectorants.

(c) Those which act as central cough suppressants, e.g. codeine and related drugs.

Experimentally, antitussives are evaluated in animals and in man by inducing artificial cough by mechanical or chemical stimulation of the respiratory tract, by electrical stimulation of the afferent autonomic nerves or by stimulation of the medullary cough centre. Results of animal studies, however, cannot be translated to actual treatment of cough in man, as cough is a symptom caused by various diseases and may also involve

considerable subjective element. Hence, careful evaluation of such remedies in actual pathological conditions in man is essential to determine their real value in therapeutics.

PHARYNGEAL DEMULCENTS

These are administered generally in the form of lozenges, troches, cough drops or linctuses. These preparations act by increasing the flow of saliva, the best natural demulcent which produces a protective and soothing effect. The 'syrup' part of most cough syrups serves the same function. Salivary secretion can be increased by such simple methods as using a few lemon drops, candy sugar, glycerrhiza or a few drops of lemon juice in a syrupy base, which are most welcome by children and elderly alike. Costly preparations like lozenges and troches containing multiple ingredients are usually unnecessary and wasteful. Demulcents are mainly useful in cough due to irritation of the pharyngeal mucosa above the epiglottis.

EXPECTORANTS

The latin word 'expectorare' means 'to drive from the chest'. Expectorants are the drugs which increase the production of demulcent respiratory tract fluid that covers and protects the irritated mucosa. These drugs are useful in the treatment of useless cough due to irritation of the respiratory mucosa below the epiglottis and respiratory conditions in which the secretion is thick and viscid, needing liquefaction. They may be useful in the therapy of chronic cough as in bronchial cough in young children and others in whom cough suppressants, particularly narcotic antitussives, are contraindicated.

Expectorants can stimulate the output of respiratory tract fluid either directly or reflexly; the latter group is also called as reflex expectorants. Certain drugs may have both these actions.

Direct stimulants : Certain volatile oils like oil of eucalyptus, anise and lemon when administered orally or by inhalation with steam, can

increase the respiratory secretions probably by a direct action. Alcohol and cedar wood oil, when added to steam inhalation, have a similar effect whereas Friar's balsam (Tincture benzoin Co.) has been found not to increase the output of the demulcent respiratory tract fluid. Large doses of creosotes and guaiacols have also been shown to possess this action in animals; and glyceryl guaiacolate forms an important ingredient of many commercially available cough mixtures. However, glyceryl guaiacolate interferes with hemostasis. Its use in the treatment of cough is of doubtful merit.

Reflex expectorants : These drugs act by stimulating the gastric reflexes which help to increase the respiratory secretions. Obviously, they produce mild irritation of the gastric mucosa and, if used in large doses, may produce nausea and vomiting. Thus, emetic drugs given in subemetic doses are said to increase bronchial secretion-producing a less tenacious sputum, easier to expectorate. Certain salts which produce such an action are called as *saline expectorants*.

(1) Saline Expectorants :

(i) **AMMONIUM SALTS** such as ammonium chloride or bicarbonate are given in a mixture form, in a syrupy base, to mask the saline taste. To get good results, they need to be given in the maximum tolerated doses. The usual dose is 300 mg. in a teaspoonful of cough mixture. The mixture, however, is not pleasant to take, smells of ammonia and may cause nausea and even vomiting. Ammonium chloride can also produce metabolic acidosis.

(ii) **POTASSIUM SALTS :** Potassium iodide is the most commonly employed preparation. It probably acts both directly and reflexly and not only increases the respiratory secretion, but has a reputation for liquefying the thick, viscid fluid. Potassium iodide is generally advocated in cough associated with chronic bronchitis, asthma and emphysema. The drug is administered orally in a dose of 300 mg. thrice daily in mixture form. The mixture has a slightly bitter saline taste. Watery solution decomposes on standing, liberating io-

dine.

Potassium iodide can cause symptoms of iodism, characterised by nasal catarrh, conjunctival swelling, edema of eyelids, lacrimation, increased respiratory tract secretions, edema and ulcers of the larynx, headache and various types of skin rashes. Chronic administration of iodides can occasionally give rise to goitre and may rarely cause hypothyroidism.

Potassium citrate is much less effective than potassium iodide and even large doses do not produce much increase in the respiratory secretions.

(2) **IPECACUANHA** is sometimes used as an expectorant. Tincture ipecacuanha is administered in a dose of 1 ml. to increase the respiratory tract fluid and to lower the viscosity of the sputum. However, it often produces nausea, vomiting and loss of appetite. Ipecacuanha contains the alkaloid emetine. (See Chapter 52).

(3) The active alkaloid, vasicine, and its derivative vasicinone, from the leaves of *Adhatoda vasica*, have been shown to possess bronchodilator and expectorant properties and the crude extract of this plant (Vasaka) in syrupy base has been used in India for ages.

CENTRAL COUGH SUPPRESSANTS

These drugs inhibit the cough reflex mainly by suppressing the co-ordinating cough centre in the medulla. They are mainly useful in the symptomatic relief of dry irritant type of cough. They are only partially successful in suppressing cough due to irritation of the carina. They, however, do reduce its intensity and the associated discomfort. They are invaluable in the treatment of cough due to pleural diseases. They can be classified into following groups:

(1) *Opioids* like codeine, noscapine and dextromethorphan.

(2) *Antihistaminic antitussives* like diphenhydramine, chlorcyclizine and dimethoxanate.

(3) *Local anaesthetic antitussives* like benzonatate. This compound is believed to produce a local anaesthetic effect on the respiratory mucosa

following its systemic absorption.

(4) *Miscellaneous antitussives* which include many compounds with different chemical structures, e.g. piperidone, ethyl dibunate and pimetine.

CODEINE : It is an alkaloid of opium and resembles morphine in its actions. Its actions, however, are much weaker. Thus 60 mg. of codeine are as much analgesic as 10 mg. of morphine. It is less constipating. Tolerance is not common and drug dependence is rare. Like morphine it depresses the cough centre and is used for this purpose. A commonly employed preparation is linctus codeine N.F. which contains 12 mg. of codeine phosphate in 4 ml. Dose : 4 ml. by mouth. It can also be used as an analgesic. It is a relatively safe drug and its only important adverse effect is constipation.

With several opioids, the dose required to suppress experimentally induced cough is lower than the analgesic dose. This has led to the belief that distinct receptors (other than the usual opioid receptors) mediate the antitussive action of opioids. Further, the antitussive action of opioids is antagonized by naloxone to a smaller extent than their analgesic action.

NOSCAPINE : It is also an opium alkaloid belonging to benzyloquinoline group. It has a smooth muscle relaxant action like papaverine. In large doses, it acts as a bronchodilator. Its antitussive action is approximately equal to that of codeine. It does not produce constipation or narcosis. Addiction does not occur. The only important side effect is occasional nausea. The antitussive dose is 15-30 mg. 3-4 times a day. It is highly effective and probably the safest antitussive.

The other synthetic compounds claimed to be specific cough suppressants include pholcodeine, dextromethorphan hydrochloride, oxeladine citrate, benzonatate, pipazethate and piperidone. There is no convincing evidence about their superiority over codeine. Generally their 'freedom from toxic effects' is overemphasized; it must be realised that the use of codeine is hardly associ-

ated with any adverse effect apart from constipation. All cough suppressants are dangerous in the presence of excessive secretions as failure to expel them may produce mechanical obstruction and atelectasis of the lung. They are also contraindicated in the presence of respiratory failure.

OTHER ANTITUSSIVES

The orally active bronchodilators are useful in the treatment of cough in the presence of bronchospasm, as bronchospasm aggravates and may even initiate cough. The drugs commonly used are salbutamol, orciprenaline, isoprenaline and ephedrine. They are discussed in detail elsewhere.

Therapeutic usefulness of antihistaminics is limited to the cases where cough is due to condition associated with post-nasal drip. They are of little value in the treatment of allergic bronchospasm and may even have a deleterious effect because of their drying effect on the bronchial secretion. The anti-histaminics with a potent sedative action may be useful in children who do not sleep because of cough, provided no contraindication to their use (such as bronchial pathology) exists. Anti-infective agents such as antibiotics are useful in controlling cough due to respiratory infections and tranquillizers can help the patients with 'nervous' cough.

Most of the proprietary preparations available as "cough remedies" generally contain a central cough suppressant, an expectorant, an antihistaminic and a bronchodilator in pleasantly flavoured syrupy base. Multiplicity of such preparations itself indicates that there is no ideal remedy for cough. Some of the ingredients present in such mixtures are no better than placebo, and those which are known to possess some pharmacological actions are generally present in inadequate amounts. The best rule, therefore, is to prescribe the simplest and the cheapest remedy of proven value and then add drugs like bronchodilators and antihistaminics if necessary, separately and in adequate doses.

MUCOLYTIC AGENTS

These drugs are used in the hope that they may make the sputum thin and less viscid, so that it can be easily expectorated. It should be noted that many patients with chest disease become dehydrated and that adequate hydration along with such simple remedies as steam inhalation can make a big difference in sputum viscosity. Finally, oxygen should never be administered without adequate humidification as dry oxygen causes drying of the respiratory mucosa. (For details, see Chapter 68).

ACETYLCYSTEINE (Airbron) : This is a derivative of a naturally occurring amino acid, L-cysteine. It reduces viscosity of sputum *in vitro*. The drug is rapidly metabolised in the body. Clinically 2-5 ml. of 10-20% solution are nebulized into a face mask every 2-8 hours to liquefy viscous tracheobronchial secretions. It is also administered by direct instillation into the tracheobronchial tree through a tracheostomy, a bronchoscope or a percutaneous intratracheal catheter. It can also be given as an aerosol.

The drug sometimes causes bronchospasm, especially in patients with bronchial asthma. Other adverse effects include fever, nausea, vomiting, stomatitis, rhinorrhoea and haemoptysis. Acetylcysteine is known to react with most metals and with rubber.

BROMHEXINE (Bisolvon) : This is a synthetic benzylamine compound of an alkaloid vasicine obtained from the plant *Adhatoda vasica*. Chemically, bromhexine is N-cyclohexyl-N-

Methyl-(2 amino-3,5-d bromobenzyl) ammonium chloride. It can be given orally, parenterally and by inhalation. Experimentally the drug has been shown to reduce the viscosity of sputum by dissolving mucopolysaccharide fibres. It is usually administered in doses of 8-16 mg. thrice daily. Adverse reactions reported so far are minor and infrequent.

PANCREATIC DORNASE, a deoxyribonuclease derived from beef pancreas, is claimed to decrease the viscosity of secretions by degrading deoxyribonucleo-protein. It acts extracellularly and does not attack living material. The preparation is claimed to be effective in changing thick, gelatinous sputum to thin milky material, when administered by aerosol.

Adverse reactions are mainly allergic and are due to sensitivity to beef protein. The therapeutic utility of this and other proteolytic enzymes such as chymotrypsin has been so far disappointing.

It must be remembered that cough serves the useful purpose of clearing the respiratory tract. It should not be severely obtunded in patients with productive cough. Use of anti-tussives in sedated or debilitated patients may prove dangerous. They should be used cautiously in the acute phase of pertussis and bronchial asthma, as inspissation of mucus plugs may contribute to fatal outcome. The possible anti-tussive effect of pain relieving drugs must be kept in mind while prescribing them in post-operative patients. *Finally, cough suppressants, especially in syrupy base, should be kept out of the reach of small children, as poisoning has been reported.*

23 Pharmacotherapy of Bronchial Asthma

Bronchial asthma is a clinical syndrome characterised by paroxysmal dyspnoea and wheeze due to increased resistance to the flow of air through the narrowed bronchi. Narrowing of the bronchi is brought about by a spasm of the bronchial smooth muscles, infiltration, edema of the bronchial mucosa and blockage by inspissated mucus within the bronchial lumen.

The precise etiology of bronchial asthma is obscure. However, it is known that inflammation and infiltration by inflammatory cells of the bronchial mucosa are important pathologic features of asthma. Against this background, attack can be triggered by various factors such as allergens, drugs, dust, cold air, exercise, chemicals and histamine. The important characteristic feature of asthma is bronchial hyper-responsiveness, an exaggerated bronchoconstrictor response to a variety of stimuli. It appears that asthma results from a complex interaction between various mediators, several cells and neural pathways. The immediate stimulus is probably the release of various mediators from a variety of inflammatory cells which include mast cells, macrophages and epithelial cells.

Majority of asthmatics (80%) are atopic, forming IgE antibody on exposure to common allergens such as house dust, mite or pollen. In such atopic subjects, challenge of the airways with allergens to which they are specifically sensitive leads to early and late phases of bronchoconstriction. The *early reaction* is rapid in onset, reaching maximum in 15-30 min. after challenge and recovering over next 24 hours. Degranulation of mast cells with mediator release is probably an important mechanism involved in early response.

Allergen provoked *late-phase* bronchocon-

striction response begins 4-6 hours after challenge and lasts for upto 24 hours; recovery may occur in a cyclical fashion. During this late phase reaction the airways become non-specifically hyper-responsive to stimuli such as histamine, which may last upto two weeks after a single allergen exposure. During this late (not early) reaction there occurs influx of neutrophils, eosinophils, macrophages in the airways and this perhaps suggests their role in the pathogenesis of the late reaction and associated increase in bronchial hyper-responsiveness. *Evidence that inflammation of the airways playing an important role in the pathogenesis of bronchial hyper-responsiveness is convincing.* Although a large number of chemical mediators are released during allergic reactions, particular attention has focused on the role of sulphido-peptide LT_3 and platelet activating factor (PAF-acether) as being mediator candidates responsible for hyper-responsiveness. These mediators are released from activated leucocytes, recruited in the airways.

It should be remembered that bronchial hyper-reactivity is only one component of asthma and that edema of the airway mucosa, exudation of plasma proteins and secretion of mucus may play an equally important role in clinical exacerbations. One of the characteristic histopathological features of asthma is disruption of the pseudostratified columnar epithelium in association with mucosal inflammation. The inflammatory cell most characteristic of asthma is the eosinophil, which may release basic proteins that are toxic to epithelial cells in the airway. Although some degree of beta-receptor dysfunction may exist in asthma, it is not clinically significant.

According to the present concept, asthma is

considered as '*Extrinsic*' when it is associated with history of atopy in patient's childhood, a family history of allergies, symptoms like hay fever, positive skin tests and raised serum IgE level. This type starts in childhood or at an early age and usually manifests clinically in 'episodic form'. As against this, the '*Intrinsic*' variety occurs in middle aged subjects with no family history of allergies and clinically it assumes 'chronic form'; in these cases the skin tests are negative and plasma IgE is not raised. This classification would appear to imply that there is an allergic factor in extrinsic asthma and none in intrinsic asthma. This is not strictly true and an allergic factor may be involved in many cases of intrinsic asthma as well.

Bronchial narrowing promotes infection distal to the obstruction. It leads to hypoxemia (reduction in arterial oxygen tension) and hypercapnia (increase in arterial CO₂ tension); both these factors may lead to acidosis, metabolic and respiratory respectively. Prolonged hypoxemia may cause pulmonary hypertension and right ventricular failure. Hypercapnia causes cerebral vasodilatation, rise in intracranial tension, mental confusion, twitching, drowsiness and finally coma. In severely ill patients, uncontrolled treatment with oxygen aggravates hypercapnia and the respiratory failure. Prolonged asthmatic attacks may also produce dehydration as the patient cannot eat or drink during the illness.

Bronchial asthma presents itself clinically in three main forms:

I. Episodic form : Here, the patient gets acute attacks, which are relieved by bronchodilator drugs with no disability between the attacks. In these cases, there is often a recognisable precipitating factor such as allergy, an upper respiratory tract infection or psychological trauma.

II. Status asthmaticus : This is a condition where an acute attack is severe, persistent, does not respond to routine treatment with adrenaline and aminophylline and is accompanied by evidence of respiratory insufficiency or failure.

III. Chronic form : This is the asthma, chronic bronchitis, emphysema syndrome, also

called chronic obstructive pulmonary disease (COPD). In this case there is more or less persistent dyspnoea and wheeze of variable severity, with acute attacks occurring from time to time. This is generally due to the presence of inflammation and thickening of mucosa of the bronchioles with resultant excessive secretion of mucus, decreased elastic recoil of the lung tissue because of destructive changes in the alveolar walls and finally hyperreactivity of the bronchi with bronchospasm. In such patients, relief of bronchospasm with drugs may be incomplete.

Principles of therapy : Asthma is much more than bronchoconstriction, and treatment must be directed toward reducing the inflammation as well as promoting bronchodilation. The various therapeutic measures available in the treatment of asthma are :

(a) *Elimination of the trigger factors* e.g. allergens, if detected. In patients in whom upper respiratory infection is known to precipitate an acute attack, prompt treatment of the infection with the proper antibiotic is essential.

(b) *Avoiding respiratory irritants* such as tobacco smoke and chemicals.

(c) *Psychological treatment* by itself is rarely of much help, except in functional cases. A sympathetic discussion of the patient's problems and a correction of his misgivings about his own disease are, however, likely to help most patients.

(d) *Drug therapy*, which forms the most important part of the management, includes the use of bronchodilators, antibiotics and corticosteroids.

(e) *Measures to correct dehydration* and acidosis, and controlled administration of oxygen.

(f) A programme of graded exercise training to improve the sense of well being and tolerance for exercise. As physical exercise tends to precipitate acute attacks in some patients, an exercise which does not precipitate such attacks (e.g. swimming) is preferred in these patients.

Antiasthmatic drugs can be classified as bronchodilators and antiinflammatory drugs.

(A) **Bronchodilators** may be classified into :

(1) Sympathomimetics :

(i) *With alpha and beta effects* : adrenaline, ephedrine.(ii) *With beta effects* : isoprenaline.(iii) *With predominantly beta₂ effects* : orciprenaline, salbutamol, terbutaline, isoe-tharine, fenoterol, carbutole and ibuteral.

(2) Theophylline derivatives.

(3) Anticholinergics.

(B) **Anti inflammatory drugs:** Corticosteroids and di-sodium cromoglycate.DRUG THERAPY DURING AN ACUTE
ATTACK

If used early, oral ephedrine may abort mild attacks. Adrenaline, isoprenaline, orciprenaline, salbutamol and aminophylline are the drugs used to treat an established acute asthmatic attack.

Beta-adrenergic agonists such as salbutamol, isoprenaline, terbutaline and adrenaline, relax the smooth muscle of all airways from trachea to the terminal bronchioles, irrespective of the spasmogen involved. They may inhibit the release of mediators from mast cells into airway and the release of acetylcholine from postganglionic cholinergic nerves. These drugs do not inhibit either the late response to allergens or the subsequent bronchial hyperresponsiveness. Airway smooth muscle in humans has only beta₂-adrenergic receptors; so do the mast cells.

ADRENALINE HYDROCHLORIDE: This is potent bronchodilator drug. Adrenaline also helps to relieve pulmonary congestion by constricting the pulmonary arteries.

It is administered subcutaneously in a dose of 0.2 to 0.5 ml. of a 1 in 1000 aqueous solution. It is effective within a few minutes. The drug is injected slowly and no further injection is made if the attack subsides.

The relief of an acute attack by adrenaline is generally dramatic but may be accompanied by unpleasant palpitation and tremulousness. To be maximally effective, it has to be injected early in an attack and hence, it is an advantage for the

patient to be able to inject it himself. This, however, carries the risk of overtreatment by the patient. *Further, before injecting the drug, one must be absolutely certain that the tip of the needle is not in a vein.*

The use of adrenaline can be dangerous in patients with cardiac asthma, hypertension, myocardial disease, hyperthyroidism, and generally in the older patients with intrinsic asthma. Use of adrenaline is especially dangerous in the hypoxic patients in status asthmaticus. Its use (and that of aminophylline) has been reported to be followed by fall in arterial oxygen tension, even when it produces a symptomatic relief. *It must be emphasized that administration of adrenaline soon after isoprenaline inhalation can cause sudden death.* Further, it can cause serious toxicity in patients receiving tricyclic antidepressants like imipramine. With the availability of more selective compounds, the use of adrenaline, isoprenaline and ephedrine is declining.

Adrenaline tends to deteriorate on storage, particularly in the presence of heat and light. *Any adrenaline solution that is even slightly coloured must not be used.*

Prolonged use of adrenaline in bronchial asthma may result in 'adrenaline resistance'.

ISOPRENALINE (Isopropylarterenol) : Isoprenaline acts similarly as adrenaline and is effective in adrenaline-resistant patients. It is administered sublingually in the dose of 10-20 mg. It is convenient to take and no special training is necessary. It acts as rapidly (2-5 min.) as adrenaline and carries the same risks as adrenaline because of its prominent cardiac stimulant action. In addition, the ease of its self administration makes it even more liable than adrenaline to overuse by the patient. Its use needs the same general precautions as that of adrenaline.

Isoprenaline can also be given by inhalation in doses of 0.1 to 0.5 ml. of 1 : 200 solution, and it relieves bronchospasm more quickly and effectively than sublingual isoprenaline. The patient, however, must be shown how to synchronize the use of the spray from nebulizer with beginning of

inspiration.

ORCIPRENALINE (Metaproterenol, Alupent): This derivative of isoprenaline is effective orally, parenterally and by inhalation. It stimulates both β_1 - and β_2 - receptors and thus resembles isoprenaline. The drug has a longer duration of action and has less cardiac stimulant action than isoprenaline. When used by inhalation, it is approximately as effective as isoprenaline. It is available as 20 mg. tablets and 0.5 mg./ml. for injection. Usually it is given orally or 0.5 - 1 mg. I.M. or S.C.

SALBUTAMOL (Ventolin, Asthalin): This β -adrenergic stimulant is chemically related to isoprenaline. It has a prominent bronchodilator (β_2 receptor action) and poor cardiac (β_1) stimulant action as compared to isoprenaline. It may not produce palpitation or rise of blood pressure in therapeutic doses. It is resistant to inactivation by COMT and, therefore, has a longer duration of action. The action of a single oral dose or single inhalation lasts for about 4-6 hours. It is more effective by inhalation (dose 100 micrograms) than by mouth (dose 2-4 mg.). It can also be given by s.c. or i.m. route in the dose of 0.5 mg. every 4 hours and i.v. slowly, in the dose of 0.25 mg. at the rate of 5-10 μ g. per minute. Because of the poor cardiac stimulant action, it is much safer than adrenaline and isoprenaline. Tremor, particularly of the hands, is an unpleasant adverse effect.

Isoetharine, terbutaline, fenoterol, carbuterol and albuterol are other β_2 agonists with similar properties as salbutamol. All can cause muscle tremor.

Inhaled β -adrenergic agonists are indicated for the short term relief of bronchoconstriction and are the treatment of choice for acute exacerbation of asthma. They are also useful for the prevention of bronchospasm, precipitated by exercise and other stimuli. Interestingly, clinically important tolerance to the bronchodilator effects of β -adrenergic agonists does not develop in patients with asthma, even after regular long term

use.

The selectivity of the beta receptor stimulants is more apparent when they are used by inhalation than orally or by injection. Further, they are likely to be ineffective in the occasional patient who, for some other reason, needs propranolol. In such a patient, aminophylline is the preferred drug.

AMINOPHYLLINE: Theophylline is a relatively weak bronchodilator at therapeutic concentration, but unlike β -adrenergic agonists it inhibits the late response to allergens. It does not inhibit the release of mediators. It may act synergistically with β -adrenergic agonist. If adrenaline fails to relieve an acute attack in about half to one hour, or if the patient is known to be adrenaline resistant, aminophylline (theophylline ethylene diamine) is administered by intravenous infusion in a dose of 5 mg/kg. over 15 - 30 minutes, followed by 0.5 - 1 mg/kg per hour for several hours. Smaller doses should be used in patients with cirrhosis, pneumonia, acute viral infection and congestive heart failure and in patients receiving cimetidine and erythromycin which interfere with metabolic degradation of drugs by the hepatic microsomal enzymes. In these situations the maintenance dose should be halved. Smokers need a larger dose. Aminophylline acts directly on the bronchial smooth muscles. It is safer than adrenaline and isoprenaline in hypoxic subjects, in status asthmaticus and in patients with concomitant cardiac disease. It is especially helpful when one cannot decide whether a given attack is one of bronchial asthma or cardiac asthma. Given rapidly, the drug may cause nausea, vomiting and collapse. Deaths have been reported following the rapid administration of intravenous aminophylline, particularly in the presence of cardiac damage. It is advisable to watch for twitching of the mouth or of the facial muscles or for severe hyperventilation which may herald the onset of an epileptiform fit. The drug can be given orally in micronized or slow release forms.

The repeated use of theophylline in children may cause learning difficulties and sleep distur-

bances.

An average acute attack is terminated within 2-4 hours by these measures and little else is necessary except liberal administration of fluids by mouth. If an attack does not respond to the above therapy, the patient should be treated as a case of status asthmaticus.

Anticholinergics : The belladonna alkaloids can induce bronchodilatation and were formerly used as a remedy for bronchial asthma. **Ipratropium bromide** is the preparation in current use; it is a congener of methyl-atropine. When administered by inhalation (40 - 80 μ g), it is as effective as 200 μ g of salbutamol by inhalation in relieving bronchial obstruction in patients with chronic bronchitis; it is much less effective in bronchial asthma. It appears to have fewer systemic adverse effects than beta adrenergic agonists as it is not much absorbed. The concurrent use of ipratropium and a beta adrenergic agonist produces additive effects.

TREATMENT OF STATUS ASTHMATICUS

Status asthmaticus is a serious medical emergency, requiring urgent hospitalization and vigorous therapy. A patient in status is markedly dyspnoeic, exhausted, cyanosed and dehydrated. He has tachycardia, may have pulsus paradoxus and may become drowsy if respiratory failure supervenes. Signs of right ventricular failure including a gallop may occur as further complications. Status asthmaticus is often precipitated by an acute respiratory infection, abrupt omission of corticosteroid therapy, reaction to inhaled allergens or to drugs (aspirin or indomethacin), metabolic acidosis or by acute emotional stress.

Relief of tachycardia and tachypnoea and evidence of better oxygenation, including a clearer mental state, should be looked for as evidences of favourable response to therapy if repeated measurements of FEV_1 are not available or are not possible because the patient is too ill to cooperate. The intensity of wheezing can be misleading; it may decrease with worsening obstruction.

(i) **Glucocorticoids** in large doses is the mainstay of therapy in a patient who has failed to respond to bronchodilators. One regime is to inject 1000 mg. of hydrocortisone as a bolus initially, followed by 4 mg/kg every 4 hours, till the patient shows distinct improvement, which may take 48 - 72 hours. Other workers would omit the initial loading dose and start injecting 250 mg. every 4 - 6 hours from the beginning of the treatment. Equivalent doses of another glucocorticoid may be used. *The bronchodilator therapy should be continued in full dose* (using aminophylline as described earlier, or either sulbutamol or terbutaline parenterally) as glucocorticoids need at least 6 hours to produce a beneficial effect. Once the patient shows definite improvement, he should be switched to oral glucocorticoids; 50 - 60 mg. of prednisolone should be given as a single morning dose. If the patient continues to improve, the dose should be reduced by 5 mg every 3 - 4 days. If it is not possible to discontinue the glucocorticoid altogether, it should be continued in the minimum possible dose. An attempt should be made to convert the patient either to alternate day glucocorticoid therapy or to beclomethasone by inhalation. The mechanism of the beneficial action of glucocorticoids in status asthmaticus is not clear. They may act in several ways stabilize the cellular lysosomal membranes, reduce the cellular stores of histamine and SRS - A, and restore the responsiveness of the airway smooth muscle to beta agonists. They do not inhibit the release of mediators nor influence their effect on the target cells.

(ii) **Other measures :** Oxygen is administered in high doses (unless there is evidence of respiratory failure) for treatment of hypoxemia. All patients in status should receive antibiotic therapy as infection is generally present. Tetracycline 250 to 500 mg. every six hours is usually preferred.

Rehydration of the patient either by mouth (using liquids to which glucose and salt have been added) or by parenteral administration of 5 per cent glucose-saline (containing appropriate quantities of potassium) is essential. It not only corrects dehydration but also makes the bronchial

secretions less tenacious. Correction of acidosis by means of intravenous sodium bicarbonate is likely to restore the patient's sensitivity to the bronchodilator drugs. Occasionally, administration of isoprenaline aerosol by positive pressure ventilation may succeed when all other measures have failed. Some of these cases would need additional measures for treating acute respiratory failure.

Sedatives, tranquillizers and antihistaminics should be avoided in status asthmaticus. Sedatives and tranquillizers make the patient drowsy, diminish his voluntary ventilatory drive and thus aggravate the anoxia. Morphine is contraindicated as it constricts the bronchi and depresses the respiratory centre.

TREATMENT OF ACUTE RESPIRATORY FAILURE

Respiratory insufficiency indicates impaired ability of the lungs to eliminate carbon dioxide or to take up oxygen. It may be obvious at rest or only on exercise. Respiratory failure is said to exist when a serious abnormality of blood gases (arterial CO_2 tension of over 50 mm Hg or arterial O_2 tension of 60 mm Hg or less) is present at rest. Respiratory failure may either be ventilatory failure or oxygenation failure. In the commoner variety of acute ventilatory failure in patients with COPD, prolonged bronchial narrowing and their obstruction by secretions are responsible for the failure in patients with already badly damaged lungs. This leads to an inadequate uptake of oxygen and inefficient elimination of carbon dioxide. Hence, the immediate need is to correct the reduced oxygen tension of the blood. Since oxygen lack stimulates the respiration reflexly, correction of this leads to a reduction of ventilation, with the result that carbon dioxide accumulates further, the patient may thus become drowsy or even comatose. To avoid this, oxygen is given continuously, preferably in a concentration of 25 - 30 per cent. (For details of oxygen therapy, see Chapter 68). This would correct the oxygen lack without reducing the ventilation.

The patient should be made to cough vigor-

ously while his chest wall is being percussed. Coughing out mucus plugs may result in significant improvement and this is further helped by humidification. Respiratory stimulants (analeptics) may be used to increase ventilation. In patients in whom oxygen therapy is followed by a reduction in ventilation, judicious use of respiratory stimulants may be useful. They may also help by stimulating coughing and thus helping the patient to remove respiratory secretions. These drugs are also used in drowsy or comatose patients along with 30 per cent oxygen. They are usually given intravenously and have to be repeated frequently. Satisfactory response is characterised by a return of deeper breathing and consciousness and a reduction in carbon dioxide tension in the blood. Later, this may be maintained by oral administration of these drugs. Excessive doses of these drugs, however, could be dangerous and may even cause convulsions. It should be realised that there is no drug which could selectively, safely and in a controlled manner stimulate the respiratory centre and the drugs offered for this purpose are neither completely reliable, nor totally devoid of adverse effects. Drugs which are generally used are nikethamide and doxapram. They are discussed in detail in Chapter 10. These drugs, however, are not useful in the long term management of patients with respiratory insufficiency. Other supportive measures in acute ventilatory failure in COPD include bronchodilators, antibiotics, large doses of glucocorticoids, a diuretic (furosemide) to treat cardiac failure and correction of acid-base and electrolyte imbalance. Initiation of digitalization may be postponed till the severe hypoxemia is corrected as cardiac arrhythmias might otherwise be precipitated. In patients who are already digitalized, maintenance doses of digoxin may, however, continue to be given. If these conservative measures do not help the patient sufficiently, aspiration of secretions from the respiratory passages through a bronchoscope or a cuffed endotracheal tube may be needed.

In acute ventilatory failure due to disorders of the central nervous system (narcotic poisoning,

stroke, head injuries), peripheral nervous system and respiratory muscles, intensive nursing care, assisted mechanical ventilation, and other life supporting measures are the mainstay of treatment. In occasional instances such as morphine poisoning, specific antidotal drug therapy may be helpful.

In the syndrome of oxygenation failure, which occurs in patients with diffuse interstitial fibrosis, there is no tendency to retention of carbon dioxide and oxygen can be administered without any reservation, safely to such patients.

PREVENTION OF ACUTE ATTACKS

Avoidance of the causal factors, such as an allergen, may lead to total elimination of acute attacks. This is not easy, and if the allergen is not easily detected, extensive skin testing and desensitisation are not likely to yield much success. Patients in whom acute attacks are precipitated by a psychologically unpleasant situation are likely to benefit from some readjustment in their family and social life; in case of children, a discussion with the parents may be helpful.

The drugs used in the prevention of acute attacks are: ephedrine hydrochloride, selective beta adrenergic agonists (already discussed), and theophylline. As the beta adrenergic agonists and theophylline act by different mechanisms to relieve bronchospasm, their concurrent use produces additive effect.

EPHEDRINE HYDROCHLORIDE : It is a sympathomimetic drug. It has been discussed in detail in Chapter 14. Given orally in the dose of 30 mg. at bed time, it is useful in preventing nocturnal asthmatic attacks. Patients who get daytime attacks need 60 mg. on waking and 30 mg. at mid-day. Ephedrine taken later in the day causes insomnia. Sometimes it causes palpitation and difficulty in passing urine, particularly in the elderly. It also raises the blood pressure in patients receiving antihypertensive drug therapy. Tolerance to ephedrine develops after several

weeks of continuous therapy but it is reversible after omission of the drug for a few days.

THEOPHYLLINE may not be tolerated orally in therapeutically effective doses (1 g. daily in divided doses) because of gastric irritation and nausea. It is used in the form of tablets. Slow release preparations of theophylline given in the evening may be useful in preventing nocturnal asthma.

TREATMENT OF CHRONIC PERSISTENT ASTHMA

Over and above the treatment during acute attack, patients with persistent asthma due to COPD need some form of maintenance therapy.

Bronchodilator drugs are generally less effective in such cases as they fail to relieve dyspnoea because they lack anti-inflammatory action. Since tolerance develops to such drugs as ephedrine and aminophylline, their efficacy often diminishes with continued use. It is better, therefore, that the patient is asked to take these drugs as and when needed and not on continuous long term basis.

Salbutamol or orciprenaline should be used (preferably by inhalation) routinely to treat acute attacks when they occur and isoprenaline reserved for resistant cases. It must, however, be emphasized that inappropriate administration of repeated doses of potent sympathomimetics can induce lethal cardiac arrhythmias.

Since chronic inflammation appears to play an important role in the pathogenesis of asthma, it is logical to suppress this process with drugs such as corticosteroids and di-sodium cromoglycate (cromolyn sodium). Unlike oral glucocorticoid therapy, steroid inhalants are highly effective in much smaller doses with marked reduction in adverse effects. Hence, steroid inhalation is now considered first-line therapy for chronic asthma. Unlike β -adrenergic agonists, steroids do not inhibit the release of mediators from mast cells in the human lung, although they do inhibit the release of mediators from macrophages and eo-

sinophils. They are useful, therefore, for blocking the late response and subsequent bronchial hyperresponsiveness. They also reduce bronchial hyperresponsiveness when given on a long-term basis. Steroids given by inhalation are more effective than orally administered steroids in reducing bronchial hyperresponsiveness, indicating a local action. Long term administration of glucocorticoids also reduces the immediate response to allergens and prevents exercise induced asthma. In addition to their anti-inflammatory action, steroids inhibit the influx of inflammatory cells into the lung after exposure to allergen. Further, corticosteroids also prevent and reverse the down-regulation of pulmonary β -adrenergic receptors.

During long term steroid therapy, the reduction in bronchial hyperresponsiveness is gradual and may take up to three months.

It appears that effective, continued and long term suppression of airway inflammation reduces the need for bronchodilator therapy, and may reduce the morbidity and, perhaps, mortality of asthma.

BECLOMETHASONE DIPROPIONATE (Becotide Inhaler): This halogenated corticosteroid ester is used in a pressurized metered inhaler which delivers 50 micrograms of the drug in aerosol form each time.

It suppresses asthma by a topical action without causing any systemic adverse reactions. The usual total daily dose recommended is 300-400 micrograms in 2-3 divided doses. Doses up to 1.5 mg. daily do not cause suppression of the hypothalamopituitary axis, and this is its major advantage. No serious adverse effects have been reported so far except for localized infection with *Candida albicans* in the mouth or the throat. However, a flare up of allergic rhinitis and nasal polyps has been reported on stopping treatment. Beclomethasone dipropionate is useful for suppressing the asthma on a long term basis where it can replace systemic glucocorticoid therapy, but it is valueless for acute attacks.

It should be introduced at an earlier stage and should become the first-line therapy for chronic

asthma.

DISODIUM CHROMOGLYCAT (Cromolyn, Ifiral, Intal): This is the sodium salt of 1,3-bis-(2-carboxychromon-5-yloxy)-2 hydroxy propane. It has been found to be useful in preventing attacks of bronchial asthma in certain selected cases.

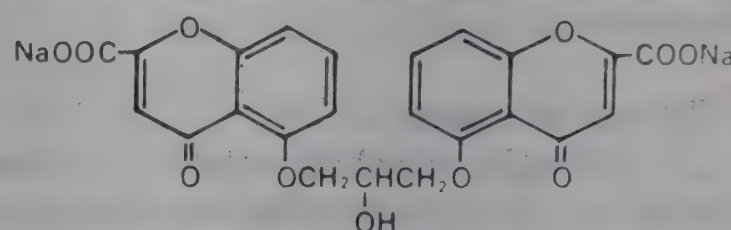


Fig. 23.1 : Disodium chromoglycate

Pharmacological actions : Cromolyn is believed to inhibit the degranulation of sensitized mast cells which otherwise occurs after a challenge by an antigen. It also prevents the late response and the subsequent bronchial hyperresponsiveness, probably by acting on inflammatory cells such as macrophages or eosinophils. Interestingly, the drug reduces certain symptoms of asthma (coughing) in some patients. It has no sympathomimetic or antihistaminic effects and it does not antagonise the pharmacological actions of SRS-A, bradykinin, acetylcholine and serotonin. However, it appears to stabilize the mast cell membrane and to inhibit release of one or more of these spasmogenic autocooids after combination of the antigen and antibody. In this respect like corticosteroids it acts as an anti inflammatory agent. It has few other significant pharmacological actions. Lastly, tolerance to cromolyn during long term use has not been reported so far.

Absorption, fate and excretion : It is absorbed poorly after oral administration (0.5%) and after inhalation (5%). The absorbed portion is rapidly eliminated unchanged in urine and bile.

Adverse reactions : Except some local irritation no serious toxicity (including teratogenic effect) has been observed with this drug so far.

Preparation and dosage : Disodium chromoglycate is administered in 20 mg. capsules, given by inhalation, 3-4 times daily. It is inhaled with the help of a special device called 'spinhaler' in which the capsule is punctured and spun by the patient's own inspiratory effort in order to release the drug. Its effect is enhanced when the patient's ventilation is improved by prior (but not simultaneous) inhalation of a beta stimulant. It is also available as powder for nasal insufflation in allergic rhinitis.

Therapeutic uses :

(1) **Allergic bronchial asthma :** When inhaled during a symptom-free interval, it protects against an attack for several hours in most patients with extrinsic asthma. It is, however, ineffective when used after the beginning of an attack. The results in patients with intrinsic asthma are less satisfactory. The reason for this is not clear. This drug has also been shown to prevent acute attacks of exercise-induced asthma. It is thus worth trying this drug in all cases of asthma not responding to conventional therapy. In general it is more likely to work in patients with clear evidence of allergic factors e.g. seasonal history, onset in early life, elevated plasma IgE levels, positive skin tests, sputum and/or blood eosinophilia and in those with exercise-induced asthma. When effective, it reduces the number of attacks, reduces cough and sputum and reduces the requirements of corticosteroids and bronchodilator drugs in the patient. Some patients have to take the drug for 3-4 weeks before they notice its beneficial effects. Cromolyn is probably the anti-inflammatory drug of first choice in children because it has few side effects. If an acute attack occurs in spite of disodium chromoglycate, it

must be treated with conventional measures.

(2) **Other respiratory allergies :** It is being tried in allergic alveolitis and in allergic rhinitis but the experience with its use in these conditions is still limited.

(3) **Miscellaneous :** The drug has also been used in the treatment of aphthous stomatitis and ulcerative colitis with variable success.

Majority of the asthmatic patients have associated chronic bronchitis and lung damage. Such cases should receive proper chemotherapy whenever the sputum turns yellow or other signs of infection develop. A few patients, who are prone to get repeated infections, may need continuous prophylactic antimicrobial therapy during winter or monsoon seasons.

Antihistaminic drugs are not useful in the treatment of asthma except in the presence of definite allergy, where they may prevent the onset of an attack. They may, however, produce drowsiness and dry out respiratory secretions. They are not advocated in the routine treatment of asthma.

Ketotifen is an antihistaminic which is claimed to be useful in asthma. It is believed to inhibit airway inflammation induced by platelet activating factor (PAF) in primate. The drug needs further studies.

Although most of the cases of asthma can now be controlled by stepwise approach using β -adrenergic agonist, steroids and theophylline, a few cases may still be difficult to manage. These may be benefited by oral glucocorticoid therapy in larger doses. In such cases, careful monitoring of patient for adverse effects is necessary (see Chapter 61).

Section VII : Cardiovascular Drugs

24 Digitalis and Pharmacotherapy of Cardiac Failure

Digitalis and the allied cardiac glycosides hold a unique position in the therapeutic armamentarium by virtue of their specific and powerful actions on the heart. These cardiotonic drugs have not found adequate substitutes in spite of extensive efforts and continue to reign supreme despite their adverse effects.

The cardiac glycosides are mainly obtained from digitalis, strophanthus and squill. A few glycosides are also present in other plants and in toad venoms.

Digitalis was first mentioned by Welsh physicians, as early as in the 13th century. In 1542, Fuchsius named the parent plant *Digitalis purpurea* from resemblance of its flower to a finger and from its purple colour. Parkinson, in 1640, was the first to describe the expectorant and the emetic actions of digitalis. He also noted that when used as an expectorant or an emetic, the compound produced variable results.

In 1776, William Withering, the master physician and botanist from Birmingham, identified digitalis as the active ingredient from a mixture of twenty different herbs used by an old woman in Shropshire for the treatment of dropsy. The old woman's medicine, according to Withering, had worked 'miracle' in a few 'hopeless' cases of dropsy. In 1785, Withering published his treatise entitled 'An Account of the Foxglove and Some of Its Medical Uses : with Practical Remarks on Dropsy and Other Diseases', which remains a classic even today. Withering clearly warned about the toxic effects of the drug. He, however, thought it to be a diuretic rather than a cardiotonic. For more than a century thereafter, digitalis was believed to be a diuretic.

In 1911, Sir James Mackenzie, along with Cushney, studied the actions of digitalis on elec-

trically induced auricular fibrillation and demonstrated that digitalis blocks the atrioventricular conduction. This work underlined the cardiac actions of digitalis.

Harry Gold in 1938 standardized the preparation digitoxin. The purified digitalis preparations were found to be much safer and more reliable than the older crude preparations and have now almost replaced them.

Electrophysiology of cardiac tissue : A knowledge of the electrophysiology of the cardiac tissue is essential for understanding the mechanism of action of cardioactive drugs. The cardiac muscle cell is surrounded by a lipoprotein membrane which behaves as if it has aqueous pores in it although no pores have actually been seen. The small chloride ions pass freely through the pores and the large phosphate and protein molecules cannot pass at all. The hydrated K^+ ion is just smaller than the pore and passes through it fifty times faster than the larger hydrated Na^+ ion. Normally Na^+ ions are concentrated extracellularly and K^+ ions intracellularly. Ordinarily, this would lead to diffusion of these ions across the cell membrane along their concentration gradients and equalization of concentrations on its two sides. Such diffusion is, however, opposed by an 'adenosine triphosphatase (ATPase) energized membrane pump system' which actively pushes Na^+ ions out of the cell and K^+ ions into the cell. For every three Na^+ ions pushed out of the cell, the pump pushes two K^+ ions into the cell and the pump is thus electrogenic. Further, during the diastole more K^+ ions leave the cell than the Na^+ ions that enter it, because of the differences in the permeability mentioned above. As these cations carry positive electrical charges, there is a net loss of positive charges from the cell during the

diastole. Thus, the inside of the resting myocardial cell remains (about 90 millivolts) negative to its outside; the cell membrane is said to be *polarized*. During spontaneous or externally induced excitation of the cell, larger quantities of Na^+ and K^+ ions cross the cell membrane. These ion fluxes are too small to be measured but show themselves by and are, in fact, responsible for the more easily measurable phenomenon of the continuously varying potential difference (*transmembrane electrical potential*) across the cell membrane. These variations in the transmembrane potential can be recorded as an action potential by inserting a microelectrode into certain myocardial cells and show the pattern (Phases 0-4) depicted in Fig. 24.1. As mentioned above, the resting transmembrane potential (RP) is negative. In 'automatic tissues', such as the SA node, because of less efficiency, the pump fails to extrude all the Na^+ ions that enter the cell; and this leads to a reduction of intracellular negativity and is at least partly responsible for the initiation of the diastolic depolarization (Phase 4, Fig. 24.1). The '*automaticity*' (i.e. the capacity for spontaneous diastolic depolarization) of different cardiac tissues depends on the slope (rapidity) of this depolarization and normally both are highest in the SA node. When this depolarization reaches a certain threshold level (T.P. in Fig. 24.1) the permeability of the cell membrane to Na^+ ion abruptly increases and large amounts of Na^+ and some calcium enter the cell passively, resulting in complete depolarization of the membrane and registering of a spike action potential (Phase 0, Fig. 24.1). Increased concentration of calcium within the cytoplasm initiates contraction of the cardiac muscle by activating myosin ATPase to provide the energy for contraction.

After the depolarization is over, repolarization occurs in several phases : (1) initial abrupt return from slight intracellular positivity almost to electroneutrality (Phase 1, Fig. 24.1). This is due to cessation of the inward Na^+ movement and commencement of K^+ efflux from the cell; (2) a prolonged plateau phase at neutral level (Phase

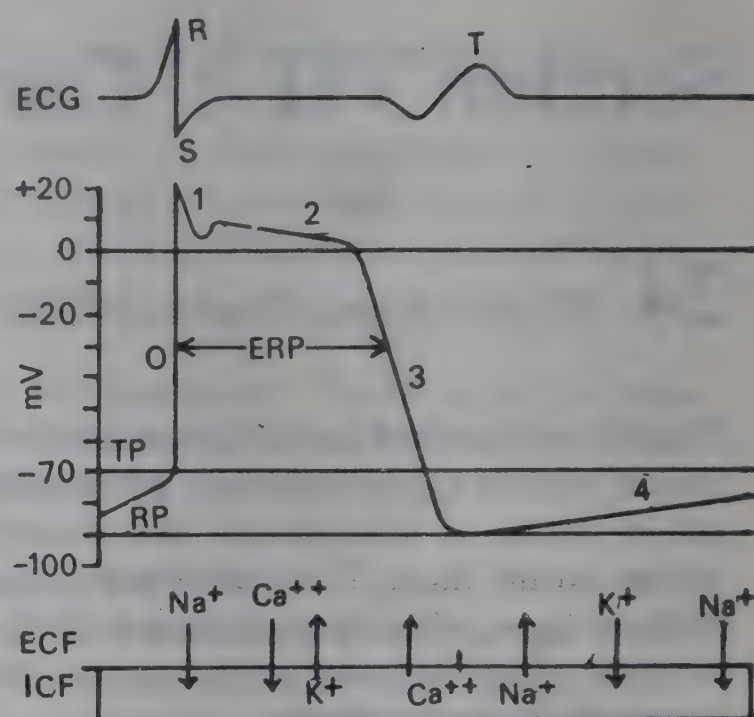


Fig. 24. 1: Relationship between transmembrane cationic fluxes, ECG recording and transmembrane action potential recorded from a mammalian Purkinje fibre.

RP = Resting potential

TP = Threshold potential

(O) Phase of depolarization

(1,2,3) Phase of repolarization

(4) Resting period exhibiting diastolic depolarization

2, Fig. 24.1). During this phase, intracellular Na^+ exchanges for extracellular Ca^{++} which thus continues to enter the cell ($\text{Na}^+ - \text{Ca}^{++}$ exchange or *slow channel* Ca^{++} entry). This calcium which enters the cell during this phase contributes importantly to the contraction of the cardiac muscle. The ST segment of the ECG coincides with this phase; and (3) a rapid but not abrupt increase in intracellular negativity to the resting transmembrane potential (Phase 3, Fig. 24.1); the T wave of the ECG coincides with the last part of this phase. During Phase 3 of repolarization, Ca^{++} is removed from the cytoplasm by reaccumulation in the sarcoplasmic sacs and by extrusion from the cell. The lowering of Ca^{++} concentration in the cytoplasm allows the cardiac muscle fibre to relax. During the entire period of repolarisation, there is a passive efflux of intracellular K^+ which repolarizes the cell membrane by establishing intracellular negativity. The P wave and the PR interval of the ECG correspond to the

spike action potential of the SA node, the atria and the AV node collectively; the QRS corresponds to the spike action potentials of the ventricles (Fig. 24.1).

During the course of the action potential, the cell has gained a little sodium and lost a little potassium. The final ionic reconstitution of the cell is achieved during the resting phase (4 in Fig. 24.1) by the ionic pump mechanism which pushes sodium out of the cell and potassium into the cell. During the greater part of the action potential, the cardiac muscle is resistant to further stimulation. The earliest transient depolarization that can be produced (without propagation) marks the end of the *absolute refractory period* (A.R.P.). The earliest depolarization that can be propagated (although with slow conduction) marks the end of the *effective refractory period* (E.R.P.). The E.R.P. is slightly longer than and includes the A.R.P. Anatomic contraction begins with phase 'O' and persists through phase '3' (Fig. 24.1).

Certain terms appear repeatedly during a discussion of cardioactive drugs and it is necessary to understand them clearly. (1) *Excitability* is the ability of a cell to respond to a stimulus by depolarization. It can be conceived in terms of the minimum intensity of a stimulus required to depolarize the cell membrane. It depends upon the level of the resting (diastolic) intracellular negativity; if the latter decreases (say from -90 to -70 mv), the excitability of the cell increases. (2) *Automaticity* is the capacity of a cell to undergo spontaneous diastolic depolarization. In the normal heart, it is maximum in the S.A. node. In the diseased heart, other areas of the myocardium increase in automaticity and become foci of ectopic impulse generation. (3) *Threshold potential* (TP) is the level of intracellular negativity at which abrupt and complete depolarization occurs. If the TP is raised (i.e. changed from -70 to -60 mv), the automaticity of the tissue is suppressed. (4) the *conduction velocity of an impulse* is determined primarily by the slope of action potential (Phase 0, Fig. 24.1) in that tissue; any

reduction in the latter leads to depression of conduction in that tissue. (5) Propagation of an impulse in a tissue depends upon (a) the ERP of the tissue and (b) its conduction velocity. (6) *Inotropic action* is the action of a drug on the contractility of the myocardium. (7) *Chronotropic action* is the action of a drug on the heart rate.

The autonomic nervous system modulates the inotropic state of the myocardium by regulating the transmembrane ion movements e.g. β adrenergic stimulation allows entry of larger amounts of Ca^{2+} through the *slow channels* and thus exerts a positive inotropic effect. β adrenergic blocking drugs counter this adrenergic influence on the heart and thus exert a negative inotropic effect. Digitalis glycosides (see later) exert their positive inotropic effect by inhibiting the Na^{+} - K^{+} pump in the cardiac cell membrane. Ca^{2+} blockers (see Chapter 27) are believed to act by blocking the entry of Ca^{2+} through the *slow channels*.

Chemistry of the cardiac glycosides : Though the official digitalis preparation is the dried leaf of the plant *Digitalis purpurea* or *foxglove*, many other plants also serve as a source of cardiac glycosides. The glycoside strophanthin is obtained from the seeds of *Strophanthus kombe* or *hispidus* and another glycoside ouabain is derived from the seeds of *Strophanthus gratus*. Other less important and less prevalent sources include squill, the dried fleshy bulb of the 'sea onion' and the plants *Convallaria majalis* and *Thevetia neriifolia*.

The active constituents of these cardiac drugs are glycosides. The cardiac glycosides exist in plants as precursors, called '*native*', '*natural*' or '*genuine*' glycosides, and these have to be subjected to a mild alkaline and enzymatic hydrolysis for the derivation of the active glycosides. The seeds of *Strophanthus gratus*, however, do not contain such precursors and yield the glycosides directly. Each glycoside represents the combination of an *aglycone* or *genin*, with a sugar. If the sugar is glucose, the glycoside is called as a

glucoside e.g. strophanthin. Structurally, the aglycone is a steroid nucleus with an attached lactone ring (Fig. 24.2). Acid hydrolysis of the glycoside results in separation of the aglycone and the sugar.

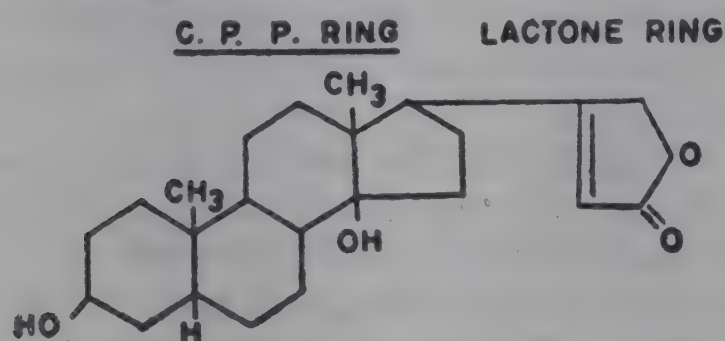


Fig. 24.2 : Structure of digitalis aglycone, digitoxigenin.

The pharmacological activity is contained in the aglycone, which has a less potent and more transient action than the parent glycoside. The sugars are postulated to confer increased water solubility, cell penetrability and potency on the aglycones. The important features of the chemistry of the cardiac glycosides are summarized in the Table 24.1.

Pharmacological actions of digitalis :

These can be divided into

- I. Cardiovascular actions and
- II. Extracardiac actions.

These are explained by a direct and an indirect action of digitalis on the heart (see Mechanism of Action).

I. Cardiovascular system : In a normal individual cardiac glycosides augment the strength and speed of myocardial contraction. This action tends to raise the cardiac output. However, in addition, the cardiac glycosides constrict the smooth muscle of the peripheral arterial and venous beds. This action tends to counteract the effects of increased force of contraction and hence, in the normal individual, digitalis in small doses fails to produce any significant alteration in the cardiac output even though the stroke volume and the mean arterial pressure may be increased.

In the presence of congestive cardiac failure, digitalis has the following actions :

(a) *Contractility* : The major pharmacologic effect of digitalis is its direct action on the myocardium. It increases the rapidity and the force of systolic contraction of the heart muscle. The more forceful contraction results in more complete ventricular emptying with a rise in stroke output. There is also an enhanced capacity to propel blood against increased peripheral resistance. At the same time, duration of the systole is abbreviated, allowing greater time for both ventricular filling and heart rest. The diastolic size of the heart is reduced. Since the oxygen consumption is a function of the initial diastolic fibre length, such a reduction in size

Table 24.1 : Important Cardiac Glycosides

Source	Precursor Glycosides	Glycoside	Sugar	Aglycone or Genin
Digitalis purpurea (leaf)	Purpurea Glycoside A (desacetyl-digilanid A)	Digitoxin	Digitoxose	Digitoxigenin
	Purpurea Glycoside B (desacetyl-digilanid B)	Gitoxin	Digitoxose	Gitoxigenin
		Gitalin	Digitoxose	Gitaligenin
Digitalis lanata (leaf)	Lanatoside A (Digilanid A)	Digitoxin	Digitoxose	Digitoxigenin
	Lanatoside B (Digilanid B)	Gitoxin	Digitoxose	Gitoxigenin
	Lanatoside C (Digilanid C, Cedilanid)	Digoxin	Digitoxose	Digoxigenin

diminishes the oxygen expenditure for a given work output. The digitalized heart, thus, can do the same work with less energy (oxygen utilization) or more work for the same energy expenditure than before digitalization. Digitalis, therefore, is called a 'cardiac tonic'. The increase in the cardiac output occurs not only in the presence of congestive cardiac failure but has also been demonstrated in cases with 'latent' heart failure, that is, in subjects with heart disease but not in failure, and in whom a significant cardiac reserve remains.

Digitalis is of limited value in 'high output' cardiac failure such as that in thyrotoxicosis, anemia, beriberi and arteriovenous fistula. In contrast, digitalis is of greater value in 'low output' failure such as that which occurs in valvular disease and in hypertensive-ischemic heart disease.

(b) *Heart rate* : In normals, digitalis produces no significant alteration in the heart rate while in an individual with congestive cardiac failure, the heart rate is reduced. If the heart rate is increased without decompensation e.g. sinus tachycardia due to fever or thyrotoxicosis, digitalis is ineffective.

Small doses of digitalis produce a decrease in the heart rate predominantly by stimulation of the vagus. This action is termed '*the vagal effect*'. It is probably evoked by sensitization of the carotid baroreceptors, but a direct central stimulant effect on the vagal nucleus cannot be ruled out. This vagal effect can be abolished by atropine, exercise or sectioning of the vagi.

Full digitalising dose also reduces the heart rate; this effect cannot be abolished by exercise or atropine and is due to direct cardiac action. In an individual with congestive cardiac failure, the sympathetic activity is increased as a compensatory phenomenon. This leads to tachycardia. Digitalis, by improving the circulation, decrease the sympathetic tone thus helping in reducing the heart rate.

(c) *Refractory period* : Refractory period is the period after onset of depolarization during

which a stimulus cannot evoke a propagated action potential and hence, a contraction. Digitalis exerts varying effects on the refractory periods of different cardiac tissues.

Digitalis causes shortening of the atrial refractory period with small doses (vagal action) and a prolongation with larger doses (direct action).

It prolongs the functional refractory period of A-V node directly and through the vagus. This leads to a decrease in the transmission of the number of stimuli arising from the supraventricular pacemakers to the ventricle. This action is of major importance in slowing the rapid ventricular rate in a patient with atrial fibrillation.

In contrast to this, digitalis shortens the ventricular refractory period by direct action. This is observed in the ECG tracing as a decrease in the Q-T interval.

(d) *Conduction velocity* : The resultant effects of the 'vagal' and the 'direct cardiac' actions on conduction are :

(i) The conduction velocity is slightly increased in the atria and the ventricles by small doses of digitalis (vagal action) while larger doses depress the conduction velocity (direct action).

(ii) Conduction through the A-V node is depressed by both vagal and direct actions, this effect being therapeutically useful.

(iii) Conduction through the Purkinje fibre system of the ventricles is depressed by the direct action.

(e) *Automaticity* : Digitalis increases the ability of the Purkinje cells and the ventricular muscle to initiate impulses. This leads to the development of ventricular extrasystoles, bigeminy, and if accompanied by depression of the conduction velocity, even to ventricular fibrillation.

(f) *Blood pressure* : Intravenous injection of cardiac glycosides in normal human subjects increases the mean arterial pressure while persons with congestive cardiac failure show no such increase. The effects of oral digitalis upon arte-

rial pressure in patients with failure are variable, and are usually secondary to improvement in the circulation.

(g) *Coronary circulation* : Improvement in coronary flow occurs secondary to the improvement in cardiac output and slowing of the heart.

(h) *Venous system* : The decrease in venous pressure in individuals with congestive cardiac failure is secondary to the improvement of circulation. Digitalis *lowers* the venous tone and increases the peripheral blood flow in individuals with congestive cardiac failure. Increased sympathetic activity probably raises the venous tone in congestive cardiac failure and digitalis-induced compensation probably restores the heightened sympathetic activity to normal.

(i) *Digitalis and potassium* : Discussed later.

(j) *Digitalis and calcium* : Calcium ions increase the force of contraction of heart. Excessive calcium ion concentration leads to cardiac arrest in systole. Digitalis acts synergistically with calcium; and digitalis toxicity is enhanced by excess of calcium ions. I.V. calcium should be avoided in individuals on therapy with the cardiac glycosides.

(k) *Effect of digitalis on the electrocardiogram (E.C.G.)* : Digitalis produces characteristic E.C.G. changes.

Changes in the T wave and ST segments are the earliest to appear, sometimes as early as within 2 to 4 hours of an oral dose. These include depression or 'scooping out' of ST segment, and inversion of the first portion of T wave. These changes may occur simultaneously or independently and may confuse the diagnosis of cardiac pathology. The changes, however, are no guide to adequacy or toxicity of digitalis dosage and severe digitalis poisoning can occur even in the absence of such changes.

Changes in the P wave and P.R. interval appear somewhat later. The P.R. interval may be prolonged, usually not more than 0.25 seconds.

The Q-T interval is shortened by digitalis, an indication that the drug shortens ventricular systole. Large doses may produce extrasystoles,

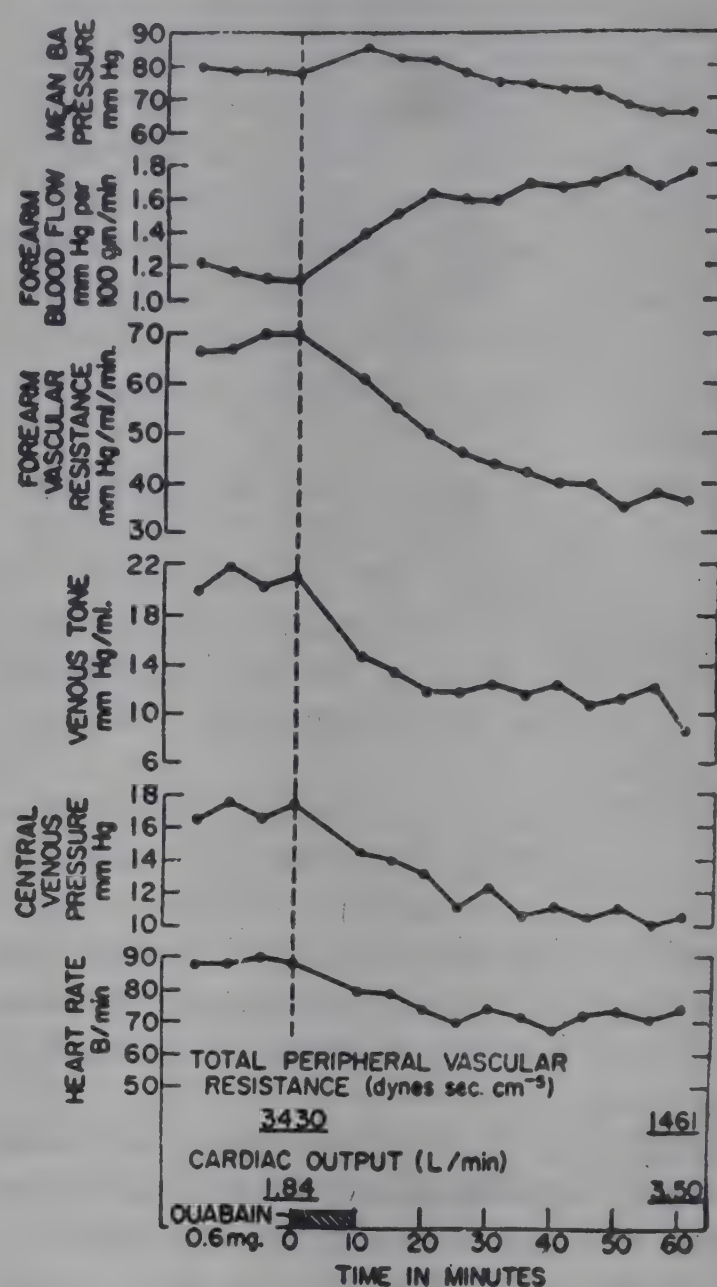


Fig. 24.3 : Serial measurements before and after intravenous ouabain in a case with rheumatic heart disease and congestive heart failure. Note the increase in the cardiac output and the forearm blood flow and the fall in central venous pressure and heart rate (Mason D.T. and Bruanwald E. : J. Clin. Invest. : 43, 532 (1964) By courtesy: Authors and Editors).

various degrees of A-V block and ventricular fibrillation as the terminal event.

Almost every type of E.C.G abnormality associated with cardiac disease has been seen in patients on digitalis. However, QRS widening in the presence of sinus rhythm is not caused by digitalis; it is due to the concurrent heart disease.

II. The extracardiac actions :

(a) *Kidney* : The fact that digitalis induced copious diuresis in individuals with 'dropsy' led Withering to believe that the drug probably acted as a diuretic.

Diuresis is often one of the first prominent manifestations of digitalis action in edematous patients with congestive heart failure. Increased excretion of sodium and water by the kidney has been demonstrated following the injection of relatively large doses of digitalis into the renal artery of a dog.

The increased urinary output in edematous patients on digitalis therapy is, however, due to :

(i) Decrease in the venous pressure bringing about shifting of the edema fluid into the circulation and

(ii) Improvement in the renal circulation resulting in an increased excretion of sodium and water by the kidney; this is secondary to increased cardiac output as well as to reduced sympathetic tone, both leading to improved renal perfusion.

(b) *The gastrointestinal tract* : Digitalis, in toxic doses, can produce diarrhoea, nausea and vomiting. The nausea and vomiting are of central origin and are probably due to stimulation of the chemoreceptor trigger zone, though a direct action on the vomiting centre has not been completely excluded.

Mechanism of action : It is now generally agreed that the positive inotropic effects of digitalis glycosides result from altered excitation-contraction coupling triggered by calcium ion. Sarcolemmal membrane structures that regulate calcium entry into the cell include the slow calcium channel, the sodium-calcium exchanger and (indirectly) sodium and potassium-activated adenosine triphosphatase and the sodium-hydrogen exchanger. By inhibiting the membrane bound sodium potassium ATPase which acts as a digitalis receptor, digitalis prevents extrusion of sodium and hastens the entry of sodium into the cell during the resting phase (diastolic depolarization). This intracellular sodium exchanges for the extracellular calcium thus increasing the in-

tracellular calcium concentration. Further, digitalis increases the calcium stores within the sarcoplasmic reticulum sacs and also permits faster release and dispersal of calcium from these sacs into the sarcoplasm. More calcium enters the cardiac cells through slow calcium channels in response to cardiac glycoside. These actions of digitalis enhance the contractility, automaticity and ectopic pacemaker activity in the heart. Decrease in the resting intracellular negativity increases the excitability of the atrial and ventricular automatic tissues. It depresses the conduction of the A-V junctional tissue by a complex mechanism.

Alterations of transmembrane fluxes of sodium and potassium following digitalis are responsible for the electrophysiological effects. Thus, inhibition of the sodium pump prevents reentry of potassium into the cell after repolarization is complete, leading to depletion of intracellular potassium. It should be noted that this potassium depleting action of digitalis is not confined to the cardiac muscle but also involves the skeletal muscle and the liver.

Finally, digitalis also exerts an indirect action on the heart, mainly by enhancing the vagal activity and thus influencing the activity of the S.A. node, the atria and the A.V. node. The consequences of this indirect action on the ventricular conducting system and on the ventricles, however, are not significant.

Absorption, fate and excretion : No fundamental differences have been found among the digitalis glycosides in their effects on heart; the dissimilarities encountered are quantitative and related to the differences in pharmacokinetics. Absorption is mostly confined to the small intestine. Absorption of the purified glycosides after subcutaneous or intramuscular administration is unreliable and local irritation may produce local tenderness, swelling and even an abscess and hence, the purified glycosides are usually administered by mouth or by intravenous injection.

The gastrointestinal absorption and fate of the purified preparations varies with the glycoside

used (Table 24.2). Digitoxin, a non polar compound, is absorbed completely and rapidly from the gut whereas the more polar digoxin is ab-

Table 24.2 : Pharmacokinetics of Oral Digoxin and Digitoxin

	Digoxin	Digitoxin
Absorption	60-85%	90-100%
Plasma Protein binding	25%	90% or more
Disposal	Renal excretion of unchanged drug	Metabolized in liver*
Enterophepatic recycling	6-8%	Extensive
Plasma half-life	24-48 hours	5 - 7 days
"Therapeutic" plasma concentration	0.5-2ng/ml	10-35 ng/ml
Time for max. effect of a single dose**	4-6 hours	6-12 hours
Persistence of effect after stopping drug	3-6 days	18 days
Time for digitalization without loading dose	5-7 days	25-30 days

* One of the metabolites is digoxin.

** Corresponding figures after I.V. dose are 1.5-3 hours (digoxin) and 4-8 hours (digitoxin).

sorbed to the extent of 80-90%. In contrast, lanatoside C (Cedilanid) is absorbed only to the extent of about 10%. Absorption of digoxin is slowed by the presence of food in the G.I. tract and by malabsorption syndrome. The digitalis glycosides are bound to plasma albumin to varying degrees. Ouabain is not bound at all. The effect of ouabain, therefore, lasts only for 1-3 days. The myocardial uptake of digitalis is reduced by reserpine, hyponatremia and hyperkalemia and is enhanced by hypokalemia.

As compared to digitoxin, digoxin is elimi-

nated primarily by the kidney. The drug is both filtered at the glomeruli and secreted by the tubules. It follows, therefore, that the digoxin excretion will be prolonged in renal insufficiency and hence the dose of digoxin needs to be reduced in renal failure.

The body eliminates per day not a fixed quantity of digitalis but a fixed proportion of that present in the body at the beginning of the day (exponential elimination). The figure is 30 per cent in the case of digoxin and 10 per cent in the case of digitoxin. This means that on repeated daily administration, digitalis will accumulate in the body until the daily dose equals the amount eliminated by the body per day. After this, a steady state is reached. It is reached much faster if initial loading doses of digitalis are employed but is eventually reached even with the use of a maintenance dose right from the first day without any initial loading dose; only it takes longer. Thus, it is possible to digitalize a patient without using any loading dose at all.

Adverse reactions : Digitalis can cause cardiac and extracardiac adverse effects.

Cardiac toxicity : Digitalis produces cardiac arrhythmias either due to *disturbed impulse formation or disturbed impulse conduction* or both. The disorders of impulse formation are due to ectopic pacemaker activity. The commonest cardiac toxicity observed in man is characterised by multifocal extrasystoles and bigemini, followed by partial or complete A.V. block. The less common manifestations include A.V dissociation, sinoatrial block, paroxysmal atrial tachycardia with block, sinoatrial arrest, ventricular tachycardia and ventricular fibrillation. In fact, any arrhythmia occurring in a patient receiving digitalis should be suspected of being due to drug toxicity until proved otherwise.

Occasionally, in chronic atrial fibrillation, digitalis toxicity is manifested by an increase in the ventricular rate, and this is mostly due to the development of paroxysmal atrial tachycardia with block (P.A.T.B.). In such cases continuation of digitalis therapy, unwittingly, to reduce

the ventricular rate may lead to death. The incidence of ventricular arrhythmias is much higher than that of atrial arrhythmias. Pre-existing extra-systoles in themselves, however, do not constitute a contraindication to digitalis therapy.

Factors which can modify the cardiac toxicity of digitalis are :

(1) *Age* : In order to avoid toxicity, an elderly patient needs a smaller dose than a young adult because of smaller muscle mass and reduced kidney function. Infants and children, on the contrary, tolerate higher plasma digoxin concentrations without any evidence of toxicity and larger doses on body weight basis can be given to them.

(2) *Route of administration and the preparation* : Intravenous and rapid oral digitalization are potentially dangerous procedures and should be undertaken only under close supervision in a hospital.

There are wide variations in the quantities of digitalis required to produce therapeutic or toxic effects in different patients and in any one patient at different times. Toxicity generally develops more easily with the slowly dissipated preparations such as digitoxin and digitalis leaf than with the rapidly excreted preparations such as digoxin.

(3) *Hypokalemia* : Loss of potassium enhances digitalis toxicity. In congestive cardiac failure, because of increased sodium retention and disturbed aldosterone metabolism, there is some degree of body potassium deficiency. Drastic restriction of dietary sodium intake plus vigorous and prolonged diuretic therapy may further increase the potassium loss. This increases the incidence of digitalis toxicity. Following excessive diuresis in a digitalised patient, digitalis cardiotoxicity may be suddenly precipitated because of further loss of potassium in the urine.

Anoxia, metabolic acidosis and prolonged exercise can produce loss of potassium through the kidney and may enhance digitalis toxicity. Nausea and vomiting may further deplete body potassium by reducing potassium intake and increas-

ing its loss by vomiting. Administration of large doses of glucose, sodium bicarbonate or insulin may precipitate digitalis toxicity by shifting the body potassium to the intracellular compartment and lowering serum and myocardial potassium.

The serum potassium level, however, is not a reliable guide to the severity of depletion of myocardial potassium. Digitalis cardiotoxicity in fact can occur even in the presence of a normal or elevated serum potassium level.

(4) *Hypercalcemia* : See digitalis and calcium.

(5) *Hypoxia* : Vigorous therapy of cor pulmonale with digitalis without correction of the pulmonary insufficiency by other specific remedies may precipitate cardiac toxicity. Cor pulmonale usually produces hypoxia which results in tachycardia and an increased blood volume due to compensatory polycythemia. Hypoxia also produces pulmonary vasoconstriction and this results in pulmonary hypertension. The right ventricle thus has to force an increased volume of blood against an increased vascular resistance (because of pulmonary hypertension) into a grossly reduced pulmonary vascular bed (due to emphysema). Inability of the right ventricle to achieve this results in right ventricular failure. Such patients might become worse following the administration of digitalis, as digitalis, by increasing the ventricular stroke volume, may further increase the load on the already inadequate pulmonary circulation. This ultimately leads to the development of gross pulmonary hypertension. Such cases, therefore, need adequate treatment with diuretics, bronchodilators, expectorants, oxygen and antibiotics. Hypoxia may also be responsible for the high incidence of digitalis toxicity seen in patients with cerebrovascular accidents.

(6) *Cardiac status* : Recent myocardial infarction increases the liability to digitalis induced arrhythmias which can occur even without the warning gastrointestinal symptoms. Further, almost any worsening of the condition of the heart or circulation from any cause increases the

sensitivity of the heart to the toxic effects of digitalis, because of the accompanying hypoxemia and acidosis. It should, however, be noted that a normal adult who accidentally takes an overdose of digitalis may not exhibit cardiac toxicity even with very large amounts of the drug. In this respect it is a poor drug to commit suicide with, as death may not occur even after swallowing 10 mg. of digoxin in a healthy adult.

Because of improved therapy, many more patients with severe chronic congestive cardiac failure are now being kept alive for longer periods. These patients have severe heart disease with diminished tolerance to digitalis; yet, they require large maintenance doses to produce a satisfactory therapeutic response. Therefore, the difference between the effective therapeutic and toxic levels of digitalis in such severely ill patients may be relatively small; in fact, the toxic dose may be reached before adequate clinical response is obtained. Furthermore, patients with severe heart failure may have renal and hepatic insufficiency and these, by reducing the excretion and detoxification of digitalis respectively, can enhance digitalis toxicity.

In patients with atrial fibrillation and congestive cardiac failure, slowing down of the ventricular rate provides a good guide to digitalis therapy. In patients with sinus rhythm, improvement in the cardiac status can occur without much reduction in the heart rate; increasing the dose of digitalis in order to slow down the heart rate to an arbitrary level in such patients can lead to digitalis toxicity. On the other hand, persistence of tachycardia and cardiac failure can be due to such factors as myocarditis, pulmonary infarcts or emboli, hypoxia or a mechanical problem such as very tight mitral stenosis. Increasing the dose of digitalis in such cases may again lead to digitalis toxicity. Many patients with cardiomyopathy tolerate digitalis poorly.

(7) *Hormones*: Adrenaline and other adrenergic drugs enhance the digitalis toxicity on heart. Digitalis toxicity is more easily provoked in hypothyroidism but is rare in hyperthyroidism.

A common cause of digitalis toxicity is the use of increasing dosage of digitalis for non-cardiac types of dyspnoea where it is not indicated at all. Unless congestive heart failure is present, digitalis is ineffective in such cases and an attempt to produce an impossible effect by increasing the dose of digitalis results in toxicity.

Gastrointestinal toxicity: Although gastrointestinal manifestations are generally the earliest toxic effects of digitalis, cardiotoxicity may sometimes occur without any gastrointestinal effects. This is especially likely to occur in potassium depleted patients. Anorexia and vomiting, which is central in origin, are the commonest symptoms. Diarrhoea is less common. It is necessary to distinguish vomiting due to digitalis from that due to cardiac failure itself.

Neurological toxicity: About 25 per cent of patients with digitalis intoxication experience a true vertigo. Visual disturbances include blurring, appearance of dancing or flickering dots and disturbances of colour vision. Headache is fairly common. Some patients complain of neuralgic pain in face, extremities and calves. Some may experience tingling and numbness in lips, tip of the nose, cheeks and ears. Lassitude, apathy, confusion, disorientation, delirium, stupor, aphasia and psychotic behaviour may appear in elderly arteriosclerotic patients.

Miscellaneous toxicity: These include skin rashes, eosinophilia and gynecomastia, and are not common.

Digitalis can cross the placental barrier producing foetal concentration higher than the maternal concentration. Massive doses of this drug to the mother, therefore, may lead to premature delivery and the newborn may present typical E.C.G. changes which persist for several days after birth.

With any digitalis preparation, approximately 60 per cent of the toxic dose is required to achieve a therapeutic effect. With gitalin, a water soluble amorphous mixture extracted from *Digitalis purpurea*, it is claimed that one third of the toxic dose is required for the therapeutic effect.

Digoxin-Quinidine interaction : When quinidine is given to a patient taking digoxin, the serum digoxin level increases. Although the magnitude of such increase is variable, on average a twofold increase has been reported. This might cause increased clinical and adverse effects of digoxin.

Others drugs which increase serum digoxin level are verapamil, methyldopa and indomethacin. Rifampicin lowers the serum digoxin level by inducing hepatic microsomal enzymes. On the other hand, antacids, kaolinpectin preparations and neomycin reduce the bio-availability of digitalis glycosides.

About 10% of patients convert large amounts of digoxin to inactive metabolites in the gut; in such patients oral antibiotics can cause a sudden increase in serum digoxin level.

Recognition of overdigitalization : Overdigitalization is to be suspected when any of the aforementioned symptoms or signs arise in a patient on digitalis therapy. A detailed analysis of the clinical situation, with special reference to past digitalization, the amount and the speed of digitalis administration during the present illness, the nature of the disease process, and the patient's electrolyte and renal status, is necessary because the electrocardiogram may not be of help in diagnosing digitalis toxicity. Digitalis therapy should be stopped immediately if toxicity is suspected.

Determination of plasma digoxin level by radioimmunoassay is a valuable tool (a) in pharmacokinetic studies; (b) in adjusting the maintenance dose of digoxin; (c) in detecting such unsuspected factors as poor patient compliance, poor bioavailability from tablets, intestinal malabsorption and increased metabolic degradation (hyperthyroidism), all of which give lower than expected plasma levels of digoxin for a given maintenance dose; higher than expected levels suggest renal failure which may otherwise go undetected unless creatinine clearance is determined and (d) in diagnosing digitalis toxicity. Therapeutic serum levels of digoxin generally

range from 0.5 to 2.5 ng/ml. Although plasma digoxin levels are higher in patients showing signs of toxicity than in those without them, one cannot rely completely on plasma digoxin level alone for the diagnosis of digitalis toxicity. A thorough clinical assessment of the patient, as mentioned above, is far more important in making this diagnosis than plasma digoxin level.

Treatment of digitalis toxicity : Digitalis is stopped and diuretic therapy is suspended. Patients with bradycardia may be treated initially with atropine. Mild toxicity (stable, ventricular premature beats or bigemini) can be treated by administration of potassium salts, 5 to 7.5 g. of potassium chloride orally, daily, in divided doses. A solution containing 40 m. equiv. of potassium chloride in 500 ml. of 5 per cent glucose can be administered intravenously over 2-4 hours with E.C.G. as a guide in more serious arrhythmias.

It must be emphasized that tachyarrhythmias and ectopic impulse generation caused by digitalis are associated with intracellular loss of potassium and can be corrected by potassium administration; however, potassium loss does not appear to be related to the other cardiac toxic actions of digitalis.

Potassium has little effect on the myocardial binding of digitalis that has already occurred; it will only reduce further uptake of the glycoside by the heart. Although it is probably the drug of choice in treating tachyarrhythmias induced by digitalis, the cation itself prolongs the refractory period of the A-V node and hence, is contraindicated in the presence of A-V block. It is usually preferred, even in the presence of normal serum potassium level, when there is an evidence of ventricular irritability, as ventricular arrhythmias appear to be related to intracellular loss of potassium from the myocardium. It must be noted that the administration of a potassium salt for treating digitalis toxicity does not counteract the positive inotropic properties of the glycoside; this, of course, is an advantage.

The supraventricular tachyarrhythmias com-

plicating digitalis therapy are best treated with a beta adrenergic blocking drug. Propranolol is used orally in the dose of 10-40 mg. every 6 hours or intravenously in the dose of 0.5 to 1 mg.

Ventricular tachycardia is best treated with either lignocaine hydrochloride or phenytoin sodium intravenously. In the case of lignocaine, an initial dose of 1-2 mg./kg. is followed either by similar doses at 20-30 minute intervals or by drip at the rate of 1-2 mg. per minute. Phenytoin sodium is injected intravenously in the dose of 250 mg. well diluted, over 3-5 minutes. Phenytoin sodium has the added advantage of countering the depression of A-V conduction by digitalis. Pharmacology of the various antiarrhythmic drugs and the treatment of A-V block are discussed in Chapter 25. Digitalis induced arrhythmias are frequently made worse by cardioversion, which is, therefore, reserved for ventricular fibrillation. In very severe digitalis intoxication (which usually involves suicidal overdose), hyperkalemia is commonly present and administration of antiarrhythmic agent may lead to cardiac arrest. Such patients are now treated with digitalis antibodies.

Preparations : The important preparations in current use are :

Digoxin tablet I.P. (Lanoxin) contains 0.125 and 0.25 mg. of digoxin. Digoxin injection is a sterile solution of digoxin in 70 per cent alcohol, each ml. of solution containing 0.25 mg. of the drug. Because both digoxin and alcohol are tissue irritants, the drug is diluted with 10 ml. of sterile 0.9 per cent sodium chloride solution and the injection is administered slowly intravenously over a period of 10 minutes.

Digitoxin tablet I.P. contains 0.1 mg. of the drug. Digitoxin injection is a sterile solution containing 0.2 mg. per ml. of digitoxin in 40 to 50 per cent alcohol.

Gitalir is a mixture of amorphous glycosides obtained from *Digitalis purpurea* and marketed in the form of 0.5 mg. tablets.

Lanatoside C (Cedilanid) is a native or precursor glycoside obtained from the leaves of *Digi-*

talus lanata. Cedilanid D is available for parenteral use only.

Ouabain I.P. is an aqueous solution for intravenous injection, which contains 0.25 mg./ml. of the drug.

Therapeutic uses : Digitalis is used in therapeutics for its inotropic effects and for its effects on the conducting system of the heart. It should be appreciated that larger doses of the glycosides are required to control arrhythmias than for treating congestive failure. The indications for digitalis therapy are :

- (i) Congestive cardiac failure (low output failure)
- (ii) Left ventricular failure
- (iii) Atrial fibrillation with tachycardia
- (iv) Atrial flutter
- (v) Atrial and A-V nodal paroxysmal atrial tachycardia.

(i) **Congestive cardiac failure :** The normal heart is capable of generating cardiac output adequate not only at rest but also during exercise and other states of increased need. In fact, the cardiac output can be increased upto 3-5 times the resting level in a normal person. A failing heart is characterized by inability to provide a cardiac output sufficient for the body's needs, initially during exercise, but later even at rest. Basically, then, heart failure is failure of the heart, the left ventricle more often than and earlier than the right ventricle, as a pump. This can arise in several ways : (1) pressure overload as in hypertension and stenosis of cardiac valves (mitral, aortic etc.); (2) volume overload as in congenital heart disease and in regurgitant lesions of the mitral and aortic valves; (3) loss of cardiac muscle due to infarction or chronic ischemic damage; (4) decreased contractility due to such causes as myocarditis; and (5) restriction of cardiac filling as in constrictive pericarditis. The syndrome of heart failure is worsened by (a) factors which increase the need for a higher cardiac output such as e.g. fever, anemia or thyrotoxicosis; and by (b) hypoxia, infection and cardiac arrhythmias.

In a failing heart, the diminished cardiac output causes fatigue, diminution in exercise tolerance and a variety of compensatory circulatory changes. Further, the increased venous pressure behind the failing ventricle is responsible for (a) pulmonary venous congestion, pulmonary edema and dyspnoea of left ventricular failure, and (b) systemic venous congestion, liver enlargement and peripheral edema of right ventricular failure.

The compensatory mechanisms which become operative in congestive heart failure are (a) cardiac hypertrophy and enlargement; (b) increased levels of circulating catecholamines due to sympathoadrenal overactivity. This causes increased contractility of the heart; tachycardia; increased peripheral resistance; re-distribution of the cardiac output with diminution in renal blood flow with all its consequences; and increased venous tone with increased venous return and increased filling pressure of the right ventricle; (c) salt and water retention by the kidneys brought about by the hemodynamic changes, and by increased plasma levels of angiotensin, aldosterone and ADH. Though by themselves beneficial, at least initially, these compensatory changes are responsible for the symptoms and signs of congestive heart failure.

The rational therapy of congestive cardiac failure would thus include : (a) rest in bed, (b) improving the cardiac function by minimum effective doses of digitalis, (c) reduction in the total body sodium by curtailing its intake and increasing its excretion by using diuretics, (d) treatment of the associated disorders such as valvular disease, rheumatic fever, cardiac arrhythmias, hypertension and infection causing or aggravating it, and (e) reduction in the afterload by using vasodilators, particularly in the treatment of resistant cardiac failure.

Digitalis, by increasing the cardiac output, brings about more complete emptying of the ventricles during systole. This reduces pulmonary congestion and edema (relief from orthopnea, disappearance of basal rales) and reduces

systemic venous pressure (resorption of the edema fluid into the circulation producing diuresis, disappearance of hepatojugular reflux). As a result of improved cardiac output, the compensatory circulation changes abate, providing further clinical relief. Thus, tachycardia improves and diuresis is established as a result of diminution in the augmented sympathetic drive and reduction in various hormonal levels in the blood.

Digitalis is *effective*, in diminishing order, in (a) congestive heart failure associated with atrial fibrillation with rapid ventricular rate; (b) congestive heart failure due to hypertension, valvular, ischemic and congenital heart disease; and (c) congestive heart failure due to myocarditis, cor pulmonale and high output cardiac states.

It is *not effective* with isolated mitral stenosis, pericardial constriction and restrictive cardiomyopathy.

It is *contraindicated* in patients with A-V block and with dynamic outflow block such as hypertrophic cardiomyopathy.

It is *useful* in shock only when there is an associated element of heart failure.

In acute heart failure associated with such catastrophies as acute myocardial infarction, acute onset mitral regurgitation and papillary muscle dysfunction, digitalis has *no place in treatment*. The treatment of these conditions is by reduction of afterload.

There has been some recent re-thinking about (a) the use of digitalis in mild congestive heart failure, and (b) the life long administration of digitalis once digitalis therapy is commenced. In the former condition, there is evidence that equally good results can be achieved by treating a patient with bed rest, salt restriction, diuretics and captopril. In the latter condition, in which digitalis toxicity is a constantly hanging sword (especially in the elderly), many feel that attempts should be made to discontinue digitalis, whenever possible, after the initial heart failure is treated, and that treatment should continue with other modalities. A wise, middle of the road, counsel may be that, "Until satisfactory data

become available, it is probably best to adhere to tested practice and use digitalis for both initial and chronic treatment of heart failure, when restriction of activity, reduced salt intake and diuresis are not sufficient" (Goodman and Gilman, 1985). However, the onus of monitoring a patient on long term digitalis therapy rests squarely on the physician.

Arrhythmias may modify the response to digitalis but they do not alter the indication for the drug if cardiac failure is present.

(ii) **Left ventricular failure** : Digitalis is helpful in the treatment of chronic pure, left ventricular failure in patients with hypertensive or ischemic heart disease and aortic valve disease. It relieves orthopnoea in these patients. It is also helpful in relieving 'nocturnal angina' (which is a manifestation of paroxysmal left ventricular failure) in patients with ischemic heart disease. If significant hypertension is present, it should naturally be treated with an appropriate antihypertensive drug.

In the treatment of acute left ventricular failure the initial drug of choice is morphine. This should be followed by parenteral administration of a rapidly acting diuretic like furosemide and digitalization.

(iii) **Atrial fibrillation** : Digitalis is indicated in patients with atrial fibrillation and rapid ventricular rate whether congestive heart failure is present or absent. It is also indicated in patients with atrial fibrillation and cardiac failure, even though the ventricular rate is not rapid.

The aim of digitalis therapy in patients with atrial fibrillation is to reduce the ventricular rate, and thus improve the circulation. If failure is present, digitalis relieves it. In the absence of failure, digitalis can protect the ventricles from the too rapid atrial impulses by depressing conduction across the A-V bundle and the A-V node. The dosage should be adjusted to maintain a ventricular rate of 60-80 per minute at rest and at less than 100 per minute with moderate exercise. In the presence of fever, sepsis, hypoxemia and hyperthyroidism, the rate cannot be brought

down to these levels and attempts to do so can only precipitate digitalis toxicity. Unlike quinidine, digitalis does not restore sinus rhythm in this condition. Addition of propranolol (10-20 mg. t.i.d.) may help to reduce ventricular rate in patients in whom digitalis alone is not effective.

Electrical cardioversion is dangerous in digitalised patients who can develop fatal ventricular arrhythmias. Digitalis should, therefore, be omitted for 2-3 days if electrical cardioversion is to be carried out in such patients.

Digitalis is not indicated in patients with atrial fibrillation with normal or slow ventricular rate if there are no symptoms or signs of cardiac failure.

(iv) **Atrial flutter** : Digitalis corrects any associated cardiac failure. Ventricular rate is slowed by augmentation of A-V block. Digitalis also prevents sudden rise in the ventricular rate during exercise and excitement. Propranolol can be added in patients resistant to digitalis alone. Atrial flutter is often converted into atrial fibrillation by digitalis, and withdrawal of digitalis at this stage may restore sinus rhythm.

(v) **Paroxysmal atrial tachycardia** : Digitalis is the drug of choice in the treatment of paroxysmal atrial tachycardia associated with cardiac failure. Physical measures such as pressure on the carotid sinus should be tried before giving digitalis. Digitalis terminates paroxysmal atrial tachycardia probably by its indirect (i.e. vagal) action. It should be noted that digitalis therapy itself sometimes converts atrial fibrillation into paroxysmal atrial tachycardia with A-V block (P.A.T.B.) and hence, it is imperative to enquire about previous digitalization before the institution of therapy. Spontaneous paroxysmal atrial tachycardia without obvious cause could be benign but P.A.T.B. induced by digitalis is a serious complication.

(vi) Except for partial and complete heart block and perhaps paroxysmal ventricular tachycardia, no other cardiac arrhythmia, unless digitalis induced, is a contraindication to digitalis therapy and it may be used if congestive cardiac

failure is present simultaneously.

Factors modifying digitalis therapy :

(a) *Myocardial infarction* : If digitalis has to be used in patients with recent myocardial infarction and C.C.F. it should be used in smaller doses than usual and the patient carefully observed for adverse effects. In such patients, treatment with a diuretic and a vasodilator is now preferred.

(b) *Presence of infection* : Digitalis may be ineffective when the causative factor of heart failure is still active, e.g. rheumatic fever or primary lung disease with infection.

(c) *Severe cardiac damage* : Digitalis is usually ineffective in correcting the failure in the presence of severe organic damage.

(d) *Body electrolyte disturbances* such as total body potassium deficiency, acidosis and chloride deficiency may diminish the efficacy of digitalis in congestive cardiac failure.

(e) *Renal function*: Digoxin toxicity is more common in patients with impaired renal function; in such patients nausea may be attributed to the uraemia and not recognised as being due to digoxin.

(f) *Thyroid dysfunction*: The ventricular rate in atrial fibrillation due to thyrotoxicosis responds poorly to digitalis. A larger dosage than is ordinarily required in the euthyroid state is necessary to reduce ventricular rate.

Digitalisation: The patient should be digitalized carefully, avoiding even the mildest digitalis toxicity. This, however, may not always be possible for reasons discussed earlier. It is now also known that the therapeutic benefit, though proportionately smaller, comes even from partial digitalization, because there is a linear dose-response relationship in the case of digitalis and there is no threshold for the positive inotropic effect of digitalis. Small or large amounts of digitalis have the same qualitative effects and similar quantitative actions proportional to the dose employed. Hence except in special circumstances, the use of initial, large loading dose of digitalis should be avoided. An initial loading dose should be used only when it is necessary to

digitalize a patient rapidly (in 24-26) hours as in case of patients in severe left ventricular failure, or acute cardiac failure due to paroxysmal atrial fibrillation with rapid ventricular rate. In patients with milder degrees of cardiac failure, especially when the patient must be treated on an out-patient or domiciliary basis, digitalis should be administered in 'maintenance' dose from the first day. The initial loading dose may be omitted when using digoxin which is the drug of choice with most workers. Some physicians, however, prefer digitoxin. Because of the long half-life of digitoxin, digitalization takes very long (4-5) weeks unless a loading dose is used; hence, it is advisable to start with a loading dose when using digitoxin. The recommended schedules for digitalis therapy with and without the initial loading dose are shown in Table 24.3. History of previous digitalis therapy should be enquired into especially before using the loading dose. A baseline E.C.G. should be recorded. Smaller than usual doses must be used in elderly subjects and in patients with renal failure. With moderate reduction in G.F.R. (50-80 ml/min) the maintenance dose of digoxin should be halved; with more severe renal failure (G.F.R. 10 ml. or less), it should be one-fourth of the usual maintenance dose. In renal failure, the loading dose of digoxin should be three times the expected maintenance dose and should be given in divided doses in the first 24 hours. Once started, digitalis therapy is generally required for life in most patients. During long term therapy with digitalis, the patient's condition should be periodically reviewed to ascertain that the maintenance dose is optimum.

Bioavailability of digoxin varies with different brands of tablets because of differences in the dissolution rates of tablets. Change to a different brand may suddenly increase the plasma level of digoxin and precipitate toxicity.

Intravenous digitalization is a potentially dangerous procedure and is to be employed only in the case of emergency. Atrial fibrillation and flutter with rapid ventricular rate and paroxysmal atrial tachycardia are the important indications

Table 24.3 : Recommended Dosage Schedule (in mg) for Digitalis Therapy

	Conventional, rapid digitalization (24 - 36 hours)		Digitalization without loading dose*	
	Dose given during first 24 hours		Maintenance dose (oral)	
	Oral	I.V.		
Digoxin	0.75 - 15	0.5 - 1.0	0.125 - 0.5	0.125 - 0.5**
Digitoxin	0.8 - 1.2	0.8 - 1.2	0.05 - 0.2	0.05 - 0.2

* Digitalization occurs in 5-7 days with digoxin and in 25 -30 days with digitoxin.

** Dosage depends upon renal function, end organ response, absorption and excretion.

for intravenous digitalization provided the patient is not already on digitalis. The preparation to be administered should preferably be diluted with isotonic sodium chloride solution and the injection should be administered very slowly. When treating a case of congestive cardiac failure, the following should be carefully observed.

I. Symptoms and signs of improvement :

- Increased urinary output.
- Relief from insomnia, orthopnoea and disappearance of basal rales.
- Diminution in jugular venous pressure and liver size.
- Disappearance of tachycardia and ventricular gallop.
- Change of dry and paper like skin to normal, moist and elastic type.

II. Symptoms and signs of toxicity :

- Anorexia, nausea and vomiting.
- Decrease in the pulse rate below 60 per minute, presence of extrasystoles or bigemini or any other arrhythmia.

Contraindications to digitalis therapy :

- The only absolute contraindication to digitalis therapy is digitalis toxicity.
- Injudicious use of digitalis is likely to prove harmful in recent myocardial infarction, partial or complete heart block including Stokes-Adams syndrome, W.P.W. syndrome, diphtheritic myocarditis, constrictive pericarditis, ventricular tachycardia, and in the presence of a tight

mitral stenosis or a grossly damaged myocardium. Digitalis, however, is indicated if congestive cardiac failure is present, but digitalization should be carried out cautiously and with small doses.

(iii) Digitalis is of no value in tachycardia due to fever, in the presence of active rheumatic fever or myxedema and in high output circulatory states such as thyrotoxicosis, anemia, beriberi and arteriovenous aneurysm. It is also of limited value in chronic cor pulmonale. The treatment, therefore, should be directed towards a medical or surgical correction of the etiology. Digitalis, however, should be used if congestive cardiac failure is present simultaneously.

OUABAIN (Strophanthin -- G): Ouabain is a pure crystalline glycoside derived from the plant *Strophanthus gratus*. Its pharmacological actions are qualitatively similar to those of digitalis. As the absorption of ouabain from the gastrointestinal tract is poor and erratic, the drug has to be administered by parenteral route.

Ouabain is often used in an emergency by intravenous route because of its very brief latent period. The action starts within 3 to 10 minutes, reaches peak within ½ to 2 hours, regresses within 8 to 12 hours and disappears totally within 24 hours to 3 days. The drug is not used for maintenance therapy.

AMRINONE (Inocor) : This bipyridine de-

rivative is a non-glycoside, non-adrenergic, positive inotropic agent. It increases the force of contraction and rate of shortening of the cardiac muscle. It probably acts by inhibiting cardiac phosphodiesterase activity and its inotropic effect is additive to those of digitalis. It has been used with beneficial effects in patients resistant to digitalis. It is administered intravenously in the dose of 0.75 µg/kg over 2 - 3 minutes. The recommended maximum daily dose is 10 mg/kg. It is also effective by mouth. A common adverse effect is dose related thrombocytopenia. Recent data regarding newer congener **milrinone** indicate that the drug has no clear benefits over digoxin.

XAMOTEROL : This drug is a partial agonist at β_1 -adrenergic receptors. It improves the ventricular contraction and decreases the ventricular filling pressure. (For details see Chapter 14).

VASODILATORS IN CONGESTIVE CARDIAC FAILURE

Reduced cardiac output in congestive cardiac failure stimulates the neurohumoral mechanisms such as sympathetic nervous system, renin-angiotensin-aldosterone system and vasopressin. This increases the systemic vascular resistance and venous return. Thus, the body tries to maintain an adequate pressure head to perfuse the vital organs. Unfortunately, such vasoconstriction of arterioles causes impedance (afterload) to left ventricular ejection and further, increases the work load of the already compromised heart. Increase in venous return increases the end diastolic ventricular filling pressure (preload), which also increases the cardiac work. A reduction in either the afterload or in the preload increases the cardiac output and has been found to be of therapeutic value, particularly in resistant cases of congestive cardiac failure.

Vasodilators have now an established place in

the management of congestive heart failure. Vasodilators are of three types : (a) predominant arterial dilators such as phentolamine and hydralazine; they reduce the afterload on the heart; (b) predominant venodilators such as the nitrates; they reduce the preload; and (c) drugs (nitroprusside, prazosin, captopril and enalapril) with a balanced, arterial as well as venous, dilator action; they reduce both afterload and preload. Captopril, in addition, reduces the secretion of aldosterone (for details see Chapter 26).

Reduction of afterload and/or preload has beneficial effects on the failing heart in resistant low output states. Thus the left ventricle functions under more favourable circumstances. Cardiac output increases, pulmonary congestion diminishes, symptoms abate and exercise tolerance improves. The drugs currently favoured in chronic congestive heart failure are : captopril (6.25 - 25 mg b.i.d.), prazosin (5 mg 8 hourly), hydralazine (50 - 75 mg 6 hourly) and isosorbide dinitrate (20 - 40 mg orally or 2.5 - 10 mg sublingually, 6 hourly). Nitroglycerine ointment can be used in place of oral isosorbide dinitrate. *Such therapy should be initiated in a hospital.*

In the management of acute congestive cardiac failure due to myocardial infarction (\pm one of its complication such as acute mitral regurgitation), the therapy of choice is an infusion of sodium nitroprusside. For details see Chapter 26. The use of nitroprusside infusion requires the facilities of an intensive cardiac care unit. In the absence of such facilities, oral nifedipine or nitroglycerine ointment may be preferred.

Vasodilator drugs are apparently useful both for fatality reduction and for relief of symptoms in patients with moderate to severe heart failure. However, it does not necessarily follow that they have these effects in patients with mild congestive heart failure. Finally, it must be remembered, that good control of heart failure is all that matters and the means by which control is achieved is unimportant.

25 Pharmacotherapy of Cardiac Arrhythmias

The drug therapy of disturbances of the cardiac rhythm (cardiac arrhythmias) has undergone a great deal of change in recent times. It is now well established that the mortality rate in acute myocardial infarction can be reduced by early recognition and prompt treatment of various arrhythmias. Anti-arrhythmic drugs are the compounds used to correct cardiac arrhythmias, while *antifibrillatory* drugs are compounds which prevent the development of atrial and/or ventricular fibrillation. The antifibrillatory drugs must be differentiated from the *defibrillatory* drugs i.e. drugs capable of restoring normal sinus rhythm of the heart under atrial and/or ventricular fibrillation. Many drugs are able to arrest rapid atrial arrhythmias and even ventricular tachycardia. However, so far no drug has been found that would consistently restore normal rhythm to a fibrillating ventricle.

The pathophysiological mechanisms responsible for the genesis of cardiac arrhythmias are not clearly understood. However, it is generally accepted that cardiac arrhythmias arise as the result either of (a) disorders of impulse formation and/or (b) disorders of impulse conduction.

Tachyarrhythmias due to disturbed impulse formation are associated with irregular and rhythmic discharge from ectopic pacemaker activity in other areas of the myocardium than the sino-atrial node. It is assumed that production of such ectopic impulse involves a defect in the spontaneous diastolic depolarization (Phase 4, Fig. 24.1), leading to ectopic areas of *automaticity*. The differences among various atrial arrhythmias could be explained on the basis of the rate of discharge of the ectopic focus. Thus, an ectopic pacemaker with a rate 160-180/min. would cause atrial tachycardia. If the ectopic rate becomes more rapid, 220-300/min., it would produce atrial flutter, while very rapid rates over 350/min. would result in atrial fibrillation.

Disorders of impulse conduction, commonly referred to as re-entry disturbances, are probably the commoner of the two mechanisms of arrhythmias. According to this theory, the affected myocardium has areas of depressed function with prolonged refractory periods. Due to this, an impulse approaching such an area would be diverted to adjacent excitable tissue. It is possible that the same impulse, after taking a circuitous route through normal tissue, will again reach the depressed area which by then becomes excitable. Upon traversing it, the excitatory process is free to re-enter normal regions and thereby to restimulate the chamber or entire heart. Repetition of this cycle is possible and would produce an ectopic tachycardia. The presence of a single re-entry mechanism within the ventricle may account for ventricular premature systoles, ventricular tachycardia and ventricular flutter. The presence of a similar mechanism within the atria, usually termed the circus phenomenon, could cause atrial flutter. It is postulated that atrial and ventricular fibrillation are caused by the fragmentation of single re-entrant path into multiple smaller cycles. A similar mechanism could reasonably explain the production of atrial or nodal tachycardia and atrial or nodal premature systoles. In arrhythmias of the re-entrant type, conduction velocity and duration of refractory period are the two most critical electrophysiological properties which could be altered by drugs with therapeutic benefits.

Clinically, it is usually not possible to determine whether an arrhythmia represents a disorder of impulse formation or impulse conduction. Identical arrhythmias on the scalar electrocardiogram may result from disparate mechanisms in different patients, or even in the same individual at different times. Hence, except in a few cases, an antiarrhythmic drug cannot be selected simply on the basis of its effect on electrophysiological

properties relative to a known clinical tachyarrhythmic mechanism.

The basic actions of antiarrhythmic drugs (Fig.25.1) are as follows: (1) Decreasing the slope of Phase 4 (diastolic depolarisation) of the action potential. This action is possessed by all antiarrhythmic drugs and suppresses the enhanced automaticity of ectopic foci. (2) Shifting the threshold potential towards zero (i.e. making it less negative). This again suppresses the automaticity of ectopic foci. Quinidine, procainamide, propranolol and potassium possess this action. (3) Shifting the resting potential away from zero (i.e. making it more negative), which also slows the rate of diastolic depolarization. Lignocaine and phenytoin possess this action. (4) Increase in the duration of the action potential, thus increasing the effective refractory period (E.R.P.) and blocking re-entrant impulses. Quinidine, procainamide, propranolol and potassium possess this action. On the other hand, lignocaine and phenytoin shorten the duration of the action potential and reduce the refractoriness of the A.V. junctional tissue. (5) Decreasing the slope of Phase 0 of the action potential and thus slowing the conduction velocity of a propagated

impulse. This action blocks the re-entrant impulses when they are responsible for an arrhythmia. Quinidine, procainamide, disopyramide and verapamil possess this action; lignocaine possesses it in large doses. Phenytoin increases the slope of Phase 0, if it is already decreased.

Antiarrhythmic drugs are generally classified according to their in-vitro electrophysiological actions:

I. Drugs which act on the initial rapid depolarization and slow the phase 0 depolarization rate. They have 'membrane stabilizing' effect. They are further subdivided into 3 groups according to their effect on action potential duration - (1a) which prolong repolarization (phase 3) and hence, slows conduction and action potential duration e.g. quinidine, procainamide, disopyramide. (1b) - which shorten repolarization (phase 3) and action potential duration e.g. lignocaine, mexiletine, tocainide and (1c) - which have no effect on action potential duration but strongly slow phase '0' depolarization rate e.g. flecainide; they markedly slow conduction. Action potential duration determines the refractoriness of the cardiac tissue.

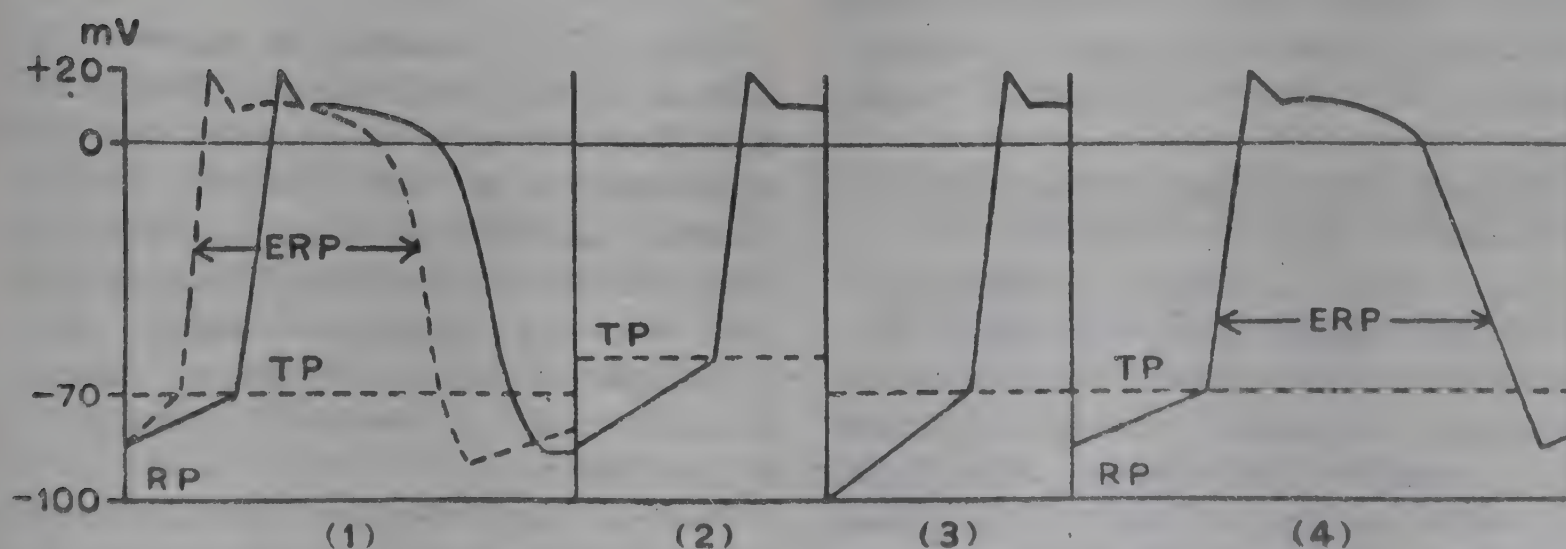


Fig. 25.1 : Diagram showing the normal pattern (dotted line) of trans-membrane action potential of a pacemaker cardiac cell and mechanisms of action of antiarrhythmic drugs: (1) Delaying the spontaneous diastolic depolarisation from the resting potential (RP), thus decreasing the rate by all drugs; (2) Increasing excitation threshold potential (TP) e.g. quinidine, procainamide, propranolol; (3) Prolonging the resting period in part by increasing maximum diastolic intracellular negativity e.g. phenytoin and (4) Increasing the effective refractory period (ERP) e.g. quinidine, procainamide.

II. Beta adrenergic blockers - which block the β_1 cardiac receptors and mainly suppress phase 4 depolarization (diastolic depolarization). They also prolong repolarization (phase 3) e.g. propranolol, particularly on long term use.

III. Drugs which act by prolonging action potential duration (prolong repolarization - phase 3) e.g. amiodarone, sotalol. Sotalol is a non-cardioselective beta blocker with additional class II activity.

IV. Calcium channel blockers - which shorten action potential duration and decline plateau (phase 2). Their action is mostly limited to nodal tissue where the electrical activities are more calcium dependent.

V. Digitalis (see Chapter 24).

Although this classification may help the clinician in rationalizing the prescription of specific drugs, it should be noted that many drugs have more than one action. The choice of anti-arrhythmic agent in a specific arrhythmia not only depends on the correct diagnosis but also on other considerations such as urgency of treatment, route of administration, extent of cardiac damage and the risk-benefit ratio of the drug concerned. All the anti-arrhythmic drugs have both cardiac and non-cardiac adverse effects which vary in severity. It must be recognized that although the drug may be indicated for a specific arrhythmia it may not be effective in every patient; this is particularly true for recurrent ventricular arrhythmias.

The drugs belonging to group I are believed to act by blocking the sodium channels.

Drugs in group 1 (a) suppress automaticity of ectopic foci; decrease conduction velocity; and prolong the refractory period. Drugs in group 1 (b) suppress automaticity; increase conduction velocity; and shorten the refractory period. These drugs impede the depolarization process without altering the resting potential and are sometimes called *membrane stabilizers* (see Chapter 12).

If a cardiac arrhythmia is precipitated by hypotension, restitution of blood pressure by vasopressor agents like noradrenaline, mephen-

termine, methoxamine and phenylephrine may establish normal sinus rhythm.

It must be remembered that not all arrhythmias need the same aggressive drug therapy. For example, sinus tachycardia and sinus bradycardia generally need no treatment other than that of the underlying cause. Only those which are lethal (ventricular fibrillation), herald more dangerous rhythm (ventricular premature beats in acute myocardial infarction) or seriously compromise cardiac output (atrial fibrillation with fast ventricular rate) require rapid and effective therapy.

Paroxysmal atrial tachycardia may be tolerated by the young but not by the old. Every patient with an arrhythmia should be evaluated for : a primary cardiovascular disorder (myocardial disease or shock); pulmonary disease; autonomic disorders (hypersensitive carotid sinus syndrome); electrolyte disturbances (acidosis, hypercalemia, hypokalemia); systemic disease; and last but not the least drug toxicity (digitalis). Correction of an identifiable factor (blood volume, afterload, preload or acidosis) should precede the administration of an anti-arrhythmic drug. However, in many situations, arrhythmias tend to be benign. Their treatment should be expectant and potentially toxic drugs should be avoided.

QUINIDINE: Quinidine, an isomer of the antimalarial drug quinine, is one of the natural alkaloids occurring in the cinchona bark. It is administered orally. The beneficial effect of quinine on atrial fibrillation was first noted by a Dutch colonial with atrial fibrillation, residing in Java, who took quinine for malaria. Later, Wenckebach, an Austrian cardiologist confirmed this observation and introduced quinine as an antiarrhythmic drug.

Pharmacological actions: Pharmacological actions of quinidine can be conveniently considered as,

- I. Cardiac actions and
- II. Extracardiac actions.

I. The cardiac actions are mainly due to its

vagolytic and myocardiac depressant properties.

Quinidine gets bound to the cardiac cell membrane and blocks the sodium channels (see Fig. 24.1) thereby modifying the various electrophysiological properties of cardiac tissue.

Automaticity : By depressing the entry of sodium into the cell during depolarization, quinidine depresses diastolic depolarization and hence, automaticity in all tissues, especially the ectopic pacemaker tissue. This depressant action on automaticity helps to suppress the arrhythmias secondary to enhanced impulse formation. Quinidine does not suppress the automaticity of the normal S.A. node although it can do so in the case of a diseased S.A. node (sick sinus syndrome).

Excitability : Quinidine depresses the excitability of the cardiac tissue and hence a weak ectopic impulse becomes ineffective.

Conduction velocity : Quinidine slows the rate of rise of the spike action potential and hence the conduction velocity in all the cardiac tissues. This property, along with the increased refractory period and decreased excitability, contributes to a decreased cardiac rate in arrhythmias due to the presence of an ectopic focus.

Refractory period : By depressing the potassium efflux during repolarization, quinidine prolongs (by a direct action) repolarization and hence, the refractory period of all cardiac tissues. However, its vagolytic action increases the atrial refractory period, shortens that of the A-V node while leaving that of the ventricles unaltered. The overall action of quinidine in the intact animal is to prolong the refractory period markedly in the atria, to increase it in the ventricles to a lesser extent and to decrease it in the A-V node. Simple prolongation of the refractory period by quinidine prevents the heart from responding to premature or rapid stimulation. Re-entry movement may also be interrupted, since the re-entrant impulse may find the originally depolarized tissue still inexcitable. Quinidine thus abolishes the arrhythmias due to circus movement.

A-V conduction : Quinidine has been shown

to depress conduction predominantly within the atria and the His-Purkinje system. However, its vagolytic effect appears to permit or even enhance conduction in the A-V node. Thus, the occurrence of sudden ventricular acceleration in patients with atrial flutter treated with quinidine is most likely to be due to both slowing of the flutter rate and improved conduction across the A-V node. Quinidine is contraindicated in the presence of intraventricular conduction disturbances.

Contractility : Quinidine exerts a negative inotropic action on the heart probably by depressing the entry of calcium ions into cardiac muscle cells. This obviously is a disadvantage.

Elevation of the serum potassium enhances the depressant effects of quinidine, while its action is reduced in the presence of hypokalemia.

There is considerable evidence suggesting that acetylcholine increases ionic efflux across the cell membrane. Quinidine, which is known to have antivagal properties, may exert its effects by blocking this action of acetylcholine.

Effects on E.C.G. : The electrophysiological effects of quinidine result in predictable alterations in the surface electrocardiogram. Early changes are characterized by increase in Q-T interval. This is probably due to an increase in the duration of ventricular systole and also due to diminished intraventricular conduction velocity. Decrease in amplitude or inversion of T wave and depression of S-T segment may also occur.

Later changes include widening and frequent notching of the P wave, and prolongation of the P-R interval.

Widening of the QRS complex signifies reduction of conduction velocity, and if accompanied by a considerable increase in the refractory period of the ventricle, might lead to the development of ventricular tachycardia and eventually to ventricular fibrillation. Quinidine, in toxic doses, may precipitate arrhythmias instead of curing them. If ventricular extrasystoles fail to respond to quinidine therapy in spite of widening of the QRS complex, further increase in quini-

dine dosage may precipitate ventricular fibrillation. The practice of withholding quinidine after the QRS complex is widened 25 to 50 per cent or above 0.12 to 0.14 second is recommended.

Quinidine is known to cause unpredictable abnormalities of rhythm in digitalized heart and as it is usually employed after initial digitalization in the treatment of atrial fibrillation, a careful surveillance of the patient is necessary.

II. Extracardiac actions :

Blood pressure : Oral or intravenous administration of quinidine in normal subjects produces a fall in blood pressure in approximately 50 per cent of the individuals. It has been suggested that the fall in blood pressure with quinidine is due to a diminished peripheral sympathetic activity and a direct relaxant action of quinidine on the arteriolar smooth muscle. Administration of quinidine in patients with cardiovascular disease causes a significant lowering of the blood pressure in most of the individuals. The subsequent circulatory adjustments, however, depend on the physiological status of the subject. Thus, if the cardiac output is normal, quinidine does not produce any significant change; but if the cardiac output is low, quinidine may shift it towards the normal. This is accomplished by a reduction in the blood pressure which reduces the left ventricular load, permitting a more complete emptying of the ventricle resulting in a rise in the cardiac output.

Quinidine, in addition to its depressant action on the myocardium, also depresses the skeletal muscle and like quinine, shows antimalarial, antipyretic and oxytocic activities.

Absorption, fate and excretion : Quinidine is almost completely absorbed from the gut. Following a single oral dose, the peak effects are reached within 2 to 3 hours and persist for 6 to 8 hours. If a higher concentration of the drug in the body is desired, the drug has to be administered at intervals of 2 to 4 hours. Quinidine given intravenously could be very toxic and hence should be used only if it is a must and then given very slowly, under E.C.G. monitoring.

Quinidine exists in the serum in a free form (40 per cent) and in a form bound to plasma albumin (60 per cent). It is primarily metabolized in the liver with half life of 5 hours and the metabolites are excreted by the kidneys; 10 to 50 per cent of the drug is excreted in an unchanged form.

With the same quinidine regimen, there are wide differences in the serum quinidine levels in different persons. Electrophysiological and toxic effects correlate better with serum levels than with dosage of quinidine; there is little correlation between reversion of arrhythmias and serum quinidine levels. These factors make frequent clinical and electrocardiographic monitoring of the patient on quinidine therapy mandatory.

Adverse reactions :

(1) Cardiac toxicity :

(a) Increasing bradycardia, conduction blocks, idioventricular rhythm and cardiac standstill.

(b) Ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation.

(c) When used in conjunction with digitalis in the treatment of atrial fibrillation or atrial flutter, quinidine may precipitate cardiac arrest or ventricular fibrillation. These are brought about by extreme depression of the S-A node and the A-V conduction, as a combined effect of quinidine and digitalis. Further it can increase plasma digitalis level and precipitate digitalis toxicity.

(d) Phenytoin shortens the half life of quinidine by as much as 50%.

(2) **Embolic phenomena :** Sudden restoration of sinus rhythm by quinidine in a patient with chronic atrial fibrillation may dislodge the mural thrombi attached to auricular appendages. This might precipitate embolic occlusion of the vessels of the vital organs and may even cause sudden death. Fortunately, this occurs very rarely and embolism is no longer considered a contraindication to quinidine therapy. Prophylactic anticoagulant therapy reduces the danger and is recommended before conversion in patients with long standing atrial fibrillation.

(3) **Heart Failure:** Quinidine sometimes may precipitate heart failure in patients with atrial fibrillation if they are not previously digitalized, more so in the presence of extensive cardiac damage.

(4) **Hypotension:** Hypotension has been observed more commonly in older patients even with relatively small doses and following I.V. administration. Postural syncope is one of the troublesome symptoms during oral quinidine therapy.

(5) **Miscellaneous toxicity:**

(a) **Intolerance :** The manifestations of intolerance include skin rashes, fever and thrombocytopenic purpura.

(b) **Cinchonism :** Under this term may be grouped various manifestations like impairment of hearing, ringing in ears, vertigo, blurred vision, light headedness, giddiness and tremor.

(c) **Gastrointestinal :** Nausea, vomiting and diarrhoea are common and put a limit on the dosage that can be used.

(d) **Cerebral :** Convulsions may result from a direct effect of quinidine on the central nervous system, particularly after its administration by the intravenous route.

(e) **Respiratory failure :** Respiratory failure may occasionally develop after intravenous quinidine administration.

Treatment of cardiotoxicity: The hypotension can be corrected by infusion of noradrenaline or other sympathomimetic vasopressor agents. Electroversion may be useful in the treatment of quinidine-induced ventricular flutter and fibrillation.

Preparations and dosage:

(1) Quinidine Sulfate I.P., tablets or capsules 200 mg. Dose 200-400 mg. every 6 hours.

(2) Quinidine gluconate injection 80 mg/ml. used for intramuscular administration. It can also be administered intravenously, slowly, diluted with 5 per cent glucose solution in a dose of 25 mg/min. The total dose should not exceed 800 mg.

Therapeutic uses:

(a) **Atrial fibrillation:** The treatment of

atrial fibrillation is modified by:

(i) the etiology: hyperthyroidism, atherosclerosis, rheumatic heart disease or hypertension,

(ii) the presence of associated cardiac pathology i.e. cardiomegaly, valvular lesions,

(iii) the type of atrial fibrillation, paroxysmal or chronic, and

(iv) the presence or absence of heart failure.

Quinidine can be used for the conversion of atrial fibrillation to normal sinus rhythm. It restores normal rhythm in 70 to 80 per cent of patients. Quinidine sulfate is administered orally in the dose of 0.2 to 0.3 g. every 3 to 4 hours for 1 to 3 days. The drug is usually not administered at night to allow undisturbed sleep. If this does not result in the restoration of the sinus rhythm, the dose may be increased to 0.4 g. every 4 hours and this regimen is continued for 3 days. Even in the absence of toxic manifestations, the total dose of 4 g. should not be exceeded. A close watch on the E.C.G. should be maintained for the development of toxic effects; however, therapy may be continued despite diarrhoea, which is a frequent side effect. Because of the toxicity of quinidine, especially in large doses, D.C. conversion is nowadays considered the preferred method of restoring sinus rhythm. When normal sinus rhythm is established, prophylactic maintenance dose, 0.2 to 0.3 g. 3 to 4 times a day is used to maintain the sinus rhythm. For a rapid effect, quinidine hydrochloride can be given intramuscularly in the dose of 0.2 to 0.4 g. It is effective in 5-15 minutes and the peak effect is seen in about 90 minutes.

Most favourable response to quinidine occurs in patients with hypertensive heart disease while those with rheumatic heart disease are the most difficult to convert. Although the ability of quinidine to convert atrial fibrillation to normal rhythm is not reduced by the duration of the arrhythmia, it is more difficult to maintain normal rhythm if the arrhythmia is of long duration. *Patients with atrial fibrillation are digitalized prior to quinidine therapy.* This is necessary because,

(i) Digitalis corrects the cardiac failure often present in association with fibrillation.

(ii) Quinidine therapy alone may result in a rapid ventricular rate during conversion of fibrillation to normal rhythm.

(iii) In atrial fibrillation where many ventricular premature beats (not due to toxic digitalis effects) are present, digitalis serves to slow the ventricular rate while quinidine abolishes premature beats.

It should be remembered, however, that both digitalis and quinidine can cause conduction blocks.

(b) **Atrial flutter** : Quinidine is much less effective than digitalis in the management of atrial flutter. Further, during the changeover from flutter to sinus rhythm at certain levels of atrial rate i.e. 250 per minute, more impulses from the atrium may be transmitted to the ventricle, resulting in serious tachycardia.

Quinidine may be combined with digitalis in cases where digitalis has slowed the ventricular rate but the atrial flutter persists.

(c) **Paroxysmal atrial and nodal tachycardia and ventricular tachycardia**: Quinidine is sometimes used in the treatment of paroxysmal nodal and atrial tachycardia to induce normal sinus rhythm. However, other measures such as carotid massage, propranolol, digitalis, verapamil, vasopressor agents and parasympathomimetic drugs should be tried first. Quinidine terminates paroxysmal supraventricular tachycardia by increasing the atrial refractory period and by suppressing the ectopic pacemaker. The dose and the route of administration are the same as for atrial flutter and fibrillation.

Quinidine is particularly useful for the treatment of paroxysmal ventricular tachycardia as against ventricular tachycardia of long standing. For this purpose, quinidine is given orally in the dose of 0.2 to 0.6 g. every 2 hours for 8 hours. After conversion, the maintenance dose is 0.2 to 0.4 g. 4 times a day for 7 days or longer by mouth. Smaller doses are used in patients in shock. The intravenous injection is hazardous and not resorted to except in emergencies.

It is dangerous to use quinidine in the presence of A-V block as it might lead to ventricular fibrillation.

(d) **Atrial, nodal and ventricular premature beats**: The vast majority of premature beats particularly if the frequency is below 100 per 24 hrs., without definite pathology, cause no complaints and require no therapy except the occasional use of sedatives. The development of ventricular premature beats during acute myocardial infarction may herald the onset of ventricular tachycardia and in such cases, quinidine therapy may be instituted in the dose of 200 to 300 mg. three to four times a day; however, the routine prophylactic use of quinidine is not advocated. Ventricular premature beats associated with atrial fibrillation may be treated with quinidine.

(e) **Ventricular fibrillation and ventricular flutter**: Ventricular flutter is a severe form of paroxysmal ventricular tachycardia and generally presages ventricular arrest or fibrillation. Drugs are useless in the treatment of these conditions and electroversion is the treatment of choice. Quinidine can, however, be used to prevent their development during surgery and recurrence after electroversion.

Contraindications to quinidine therapy :

(a) History of quinidine intolerance.

(b) Ventricular tachycardia associated with complete A-V block.

(c) Stokes-Adams syndrome.

(d) Hypotension.

Quinidine should be given with caution in bundle branch block and in extensive myocardial damage as suggested by gross cardiomegaly. Quinidine must not be used to treat digitalis-induced arrhythmias.

PROCAINAMIDE (Pronestyl): It was demonstrated that topical application of procaine to the heart suppresses the excitability of the ventricular muscle. The disadvantages of procaine, however, are that it is not effective orally and it produces stimulation of the central nervous system resulting in convulsions if allowed in

excess into the blood stream. Further, the action is of short duration as it is broken down by an esterase in the plasma (probably identical with the pseudocholinesterase).

Procainamide is effective by oral, intramuscular and intravenous routes, is not destroyed by esterase, and is almost free from toxic effects on the central nervous system. The local anaesthetic properties of procainamide are comparable to those of procaine but it does not produce nerve block.

Pharmacological actions:

(1) **Cardiac effects:** These are qualitatively identical with those of quinidine.

(2) **Hemodynamic effects:** These effects are primarily due to the depressant action of the drug on the myocardium and are similar to those of quinidine.

The drug induces a moderate fall in blood pressure; this action, however, may be marked if the blood pressure is already low.

(3) **Effects on the E.C.G.:** They are similar to those following quinidine.

Absorption, fate and excretion: Procainamide is rapidly and almost completely absorbed from the gastrointestinal tract. After oral administration, peak plasma level is reached within 1 hour and declines by 4 hours. Intramuscular administration produces peak level within 5 to 30 minutes and the level gradually declines by 6 hours. Peak level with intravenous route is reached within 4 minutes.

Unlike quinidine, it is only minimally bound to plasma proteins and is largely (60%) excreted unchanged in urine. A small part is hydrolysed by plasma esterases.

Impairment of renal function can produce cumulative procainamide toxicity.

Adverse reactions:

(1) Manifestations of intolerance include chills, fever, itching, skin rash and angioedema.

(2) Cardiotoxicity is similar to that of quinidine.

(3) Hypotension (leading to coronary insufficiency, or a shock-like state) occurs most often

with the intravenous use.

(4) Mental symptoms simulating psychosis develop occasionally.

(5) Gastrointestinal effects such as anorexia, nausea and vomiting.

(6) Agranulocytosis and systemic lupus erythematosus are serious manifestations.

Preparations: Procainamide hydrochloride (Pronestyl) tablet N.F. 250 mg.

Procainamide hydrochloride injection I.P. contains 100 mg. of procainamide per ml.

Methods of administration:

(a) **Oral method:** Preferred method, 0.25 to 0.5 g. every 4 to 6 hours. In serious cases, 0.5 to 1 g. may be administered every 2 to 4 hours. The maintenance dose is 0.25 to 0.5 g. 6 hourly.

(b) **Intramuscular administration:** 0.25 to 0.5 g. every 4 to 6 hours. Procainamide hydrochloride or procainamide gluconate are the preparations used.

(c) **Intravenous administration:** After initial dose of 100 mg., 100 mg. may be injected every 4 minutes, the total dose not exceeding 1 gm. This route is indicated when conversion to normal sinus rhythm is urgent, as in shock-like states and during surgery. A constant watch on the E.C.G. and blood pressure is essential. Fall in blood pressure should be countered by the administration of vasopressor agents.

Therapeutic uses: Procainamide is valuable substitute for quinidine in the acute setting when the latter drug is not tolerated. It is more effective in ventricular arrhythmias than in atrial ones. It is not useful in long term treatment because of the high risk of lupus erythematosus.

(1) **Atrial and nodal premature beats and paroxysmal atrial tachycardia:** Procainamide can be used in the treatment of paroxysmal atrial tachycardia in place of quinidine.

(2) **Ventricular premature beats and ventricular tachycardia:** Procainamide abolishes ventricular extrasystoles and controls ventricular tachycardia in approximately 70 per cent of the cases.

Prophylactic use against ventricular tachycar-

dia or fibrillation following myocardial infarction is justified only in the presence of repeated and multifocal extrasystoles and not routinely, as it is a myocardial depressant. It may be used prophylactically in patients who are undergoing cardiac catheterization or surgery and have a preexisting arrhythmia or are prone to develop arrhythmias.

(3) **Ectopic rhythms during digitalis toxicity:** Procainamide is often efficacious in the therapy of ectopic beats due to digitalis toxicity.

(4) Procainamide may be useful in patients in whom quinidine produces cinchonism.

The electrophysiological effects, both beneficial and toxic, of procainamide and quinidine are additive.

FLECAINIDE: This fluorinated analogue of procainamide is well absorbed on oral administration. It is highly effective in arrhythmias that are not associated with an increased risk of sudden death, such as isolated ventricular ectopic beats in patients with normal left ventricular function. In contrast to quinidine and procainamide, it causes marked prolongation of PR and QRS intervals and minimal changes in the QT interval. It has moderate negative inotropic effect. It is given orally, in twice daily doses.

ENCAINIDE : It has properties similar to flecainide and is effective orally. It has mild negative inotropic action. Both flecainide and encainide are used as substitute for quinidine.

DISOPYRAMIDE PHOSPHATE (Norpace): This drug has membrane depressant and anticholinergic properties. Its therapeutic effects and toxicity are similar to those of quinidine but it is better tolerated. Given orally, it is completely absorbed and has a plasma half life of 6 hours. About 70% of the drug is excreted in urine and the rest in the bile. It can also be given intravenously. Common adverse effects include prominent anticholinergic effects such as dryness of mouth, retention of urine, and constipation;

and less common are mental depression, impotence and hypotension. Worsening of heart failure due to depression of myocardial contractility, increase in the ventricular rate in patients with atrial fibrillation, worsening of A-V block and ventricular arrhythmias are its serious adverse effects. It is most useful in the ventricular arrhythmias and to a smaller extent in the atrial arrhythmias. It is contraindicated in the presence of acute pulmonary edema, untreated cardiac failure and shock. Caution must be exercised in patients with glaucoma and in those with prostatic enlargement. The recommended oral dose is 100-150 mg. four times daily, upto a maximum of 1600 mg. daily. Because of its toxicity, the use of disopyramide should be limited to patients who do not respond to quinidine and procainamide.

POTASSIUM: The basic effects of potassium administration without causing hyperkalemia are: reduction in conduction velocity, prolongation of the refractory period and diminution in the automaticity. These effects differ in degree in different cardiac tissues and are most marked in the Purkinje fibres. In toxic doses, it is more likely to cause intraventricular conduction defects than AV block. Hypokalemia predisposes to digitalis toxicity; this is discussed in detail in Chapter 24. Slight, induced hyperkalemia has been shown to protect against arrhythmias arising after cardiac surgery (also see Chapter 33). Correction of hypokalemia, hypoxia and acid base disturbances can often restore sinus rhythm without the use of anti-arrhythmic drugs.

The administration of antiarrhythmic agents in the presence of high serum potassium levels may be disastrous.

LIGNOCAINE (Lidocaine, Xylocard): This drug, a local anaesthetic, depresses diastolic depolarization and automaticity in ventricular tissue. Unlike procainamide and quinidine it has little influence on the conduction velocity of normal tissues. It shortens the ventricular action potential. The electrophysiological function of

the atria, S-A node and A-V node is not much affected. Further, it has a rapid onset of action; toxicity, if it occurs, is usually of short duration. Since the electrophysiological effects of lignocaine are primarily limited to ventricular myocardium, it is most useful in abolishing ventricular arrhythmias. Its lack of action on atrio-ventricular, nodal conduction velocity, makes it a suitable drug in the treatment of digitalis induced ventricular arrhythmia. Unlike quinidine, lignocaine produces hardly any effect on the surface electrocardiogram.

The drug is usually given intravenously, although it can also be used intramuscularly. The intravenous preparation does not contain a preservative, sympathomimetic or other vasoconstrictor. The common local anaesthetic preparation should not be used intravenously. Its plasma-protein-binding is minimal and it is rapidly metabolized in the liver. The plasma half-life of a single injection is very short ranging from 15-

30 min. It is, therefore, given by an initial I.V. bolus, followed by a continuous I.V. infusion. In recommended dosage, lignocaine is a relatively safe drug. It should be used cautiously in the presence of liver damage.

The adverse effects include drowsiness, disorientation, muscle twitchings and convulsions. It diminishes the cardiac output and may rarely cause hypotension, bradycardia and apnea. An intravenous preparation of a barbiturate or diazepam should be at hand while using intravenous lignocaine.

Therapeutic uses: Lignocaine is the drug of first choice for treating severe ventricular arrhythmias of many etiologies in an acute setting. It is preferred to quinidine and procainamide in the treatment of digitalis induced ventricular tachycardia. The risk of producing hypotension and cardiac standstill is small. It is the drug of choice in the emergency termination of ventricular tachycardia following recent

Table 25.1 : Principa Effects of Antiarrhythmic Drugs on the Heart

	Group IA (Quinidine, Procainamide, Disopyramide)	Group IB (Lignocaine, Phenytoin)	Group II (Propranolol)	Group III (Verapamil)
Electrophysiological				
Automaticity	Decrease	Decrease	Decrease	Decrease
Excitability	Decrease	No change	Decrease	Decrease
Conduction velocity	Decrease	No change or increase	Decrease	Decrease
E.R.P.	Increase	Decrease	Increase	Increase
Electrocardiogram				
P. R. duration	No change or increase	No change or decrease	No change or increase	No change or increase
QRS duration	Increase	No change	No change	No change
Q-T duration	Increase	No change or decrease	No change or decrease	No change
Hemodynamic				
Blood pressure	No change or decrease	No change or decrease	No change or decrease	No change or decrease
Cardiac output	Decrease	No change or decrease	Decrease	Decrease
Contractility	Decrease	No change or decrease	Decrease	Decrease
Left ventricular end diastolic pressure	May increase	No change or increase	May increase	May increase

myocardial infarction and that occurring during cardiac surgery and cardiac catheterization. It is also used prophylactically to prevent ventricular arrhythmias during electroversion. Because of its immediate and short duration of action (10 min.), lignocaine is most often given as a single large initial intravenous bolus, 1-2 mg./kg. in 30 sec., followed by a continuous intravenous drip at the rate of 1-4 mg/min. to maintain the effect. Smaller doses (50%) are used in patients with congestive heart failure, shock, hepatic dysfunction and in those over 70 years of age. The risk of ventricular fibrillation with death is highest in the first few hours after the onset of an attack of myocardial infarction. An intramuscular injection of 400 mg (13.3%, 3 ml) of lignocaine, given immediately after an attack, has been shown to be effective in preventing this lethal complication. The effect lasts for about 1 1/2 hour; this period is generally sufficient to transport the patient to an intensive care unit in a hospital. The drug also prevents paroxysmal ventricular tachycardia in this setting. It is safe and its use may be life saving.

MEXILETINE: This drug resembles lignocaine, chemically as well as in its pharmacological effects. It is, however, effective orally and hence, can be used prophylactically for prevention of ventricular arrhythmias. The dose is 400 mg. followed by 200 mg. 3-4 times, daily.

TOCAINIDE: This is an amine analog of lignocaine and can be given orally in the dose of 400-800 mg. every 8 hrs. Peak plasma level is reached in 1-4 hr. It can cause dose related neurological adverse effects such as twitching, tremors, diplopia and hallucinations.

PHENYTOIN SODIUM. (Diphenylhydantoin): The hypothesis that the excitatory processes or substances initiating the discharge of impulses in cardiac arrhythmias may be similar in some fundamental property to those responsible for epilepsy, led to the use of diphenylhydantoin in the treatment of cardiac arrhythmias.

Diphenylhydantoin depresses the ventricular automaticity; but unlike quinidine and procainamide, it does not decrease the conduction velocity between the ventricular fibres. It also accelerates the A-V conduction. Similar to lignocaine it reduces the duration of the action-potential. Phenytoin has little effect on the surface electrocardiogram although it may shorten the QT interval. It can be administered orally in the dosage of 100 to 200 mg. 4 times daily for the suppression of ectopic beats and for prophylaxis against recurrent paroxysmal tachycardia. In the treatment of rapid supraventricular or ventricular tachycardia it is given by intravenous bolus injection of 100 mg. every 5 min. (total dose 10-15 mg/kg) to produce a quick effect. Because of its long half-life, the therapeutic effect can be maintained by oral administration of 1.0 g. on the first day, 0.6 g. on the second and third days and 0.4 g. per day thereafter. It is usually not given by constant I.V. infusion due to the high incidence of phlebitis caused by its alkaline pH.

Large intravenous doses may cause marked hypotension, A-V block and cardiac arrest.

Therapeutic uses: The main use of intravenous phenytoin is to terminate digitalis induced cardiac arrhythmias where it is preferred as it does not aggravate the A-V block. (But, even here, lignocaine is more effective than phenytoin.) Nor does it cause any adverse effect on intraventricular conduction or myocardial contractility. The reversibility of the adverse effects and freedom from hypotension after therapeutic doses are important advantages over other antiarrhythmic agents.

In digitalis-induced ventricular tachycardia, when procainamide has to be discontinued because of QRS widening, diphenylhydantoin can still be used since it can reverse the conduction block while accentuating the depression of automaticity.

Its use in controlling arrhythmias is disappointing unless they are digitalis induced.

Toxicity of phenytoin sodium is discussed in detail in Chapter 7.

Sympathetic Blocking Agents: Alpha-

adrenergic blocking drugs like phenoxybenzamine administered prophylactically, can prevent the cardiac arrhythmias occurring in the deeper planes of cyclopropane anaesthesia. They, however, are unable to reverse the arrhythmia if it has already occurred.

PROPRANOLOL: Myocardial sympathetic β -receptor stimulation increases automaticity, enhances A-V conduction velocity and shortens the refractory period especially in supraventricular tissues. Propranolol, a β -adrenergic blocking agent can reverse these effects. It also has a direct quinidine like membrane stabilizing action in large doses. These combined antiadrenergic and direct actions cause decreased automaticity and conduction velocity and increased refractoriness; the refractory period is prolonged. 1-Propранолol antagonises the tachyarrhythmias precipitated by sympathetic discharge during exercise, emotion or anaesthesia and in patients with pheochromocytoma. Further, propranolol is a useful adjunct in patients with atrial fibrillation and flutter refractory to digitalis. In patients with atrial fibrillation and W.P.W. syndrome, propranolol is used instead of digitalis because in such patients digitalis tends to increase the ventricular rate.

The detailed pharmacology and toxicity of β -adrenergic receptor blocking drugs is discussed in Chapter 14. The plasma half life of propranolol is relatively short (2-3 hours) following I.V. administration and 4-6 hours after oral use. Severe propranolol toxicity may result in progressive bradycardia and cardiac asystole. The drug is given slowly I.V. at the rate of 1 mg. every 5-10 min. upto a total dose of 0.1 mg./kg. Orally it is used in the dose of 10-40 mg. every 6-8 hours. Other beta-blockers can also be used for similar purposes.

Beta blockers may potentiate the negative inotropic action of antiarrhythmic drugs, particularly prenylamine and verapamil, which can result in marked bradycardia and even asystole.

Cholinergic and anticholinergic drugs : Acetylcholine decreases the automaticity by de-

pressing the slope of spontaneous diastolic depolarization and lowering the resting membrane potential. It also slows conduction through the A-V node, increases its refractory period and may cause A-V block. These effects are seen following vagal activation. **Edrophonium**, a short acting cholinesterase inhibitor, is sometimes useful in the treatment of supraventricular arrhythmia. It acts by preventing the destruction of acetylcholine.

Atropine, an anticholinergic drug, blocks the effects of vagal stimulation. It is of some value for the diagnosis of sinus bradycardia, where it increases the heart rate, and in the treatment of heart block, if the latter is due to vagal influences. Its indiscriminate use to treat sinus bradycardia after acute myocardial infarction may precipitate ventricular arrhythmias because the sympathetic activity is no longer moderated by vagal influences.

VERAPAMIL (Isoptin, Cordilox): This blocker of calcium ions through the slow channels is discussed in detail in Chapter 27. It is the drug of choice for rapid conversion to sinus rhythm in cases of paroxysmal supraventricular tachycardia, where it is given intravenously in the dose of 10 mg injected over a period 2-3 minutes; the dose can be repeated, if necessary, after 30 minutes. Verapamil (oral or I.V.) can also be used to reduce the ventricular rate in patients with atrial fibrillation and atrial flutter. I.V. verapamil is absolutely contraindicated in patients on betablockers, quinidine or disopyramide.

Amiodarone: This drug, structurally related to thyroxine, is used to treat refractory supraventricular and ventricular tachyarrhythmias. It possesses antiadrenergic properties. It depresses sinus, atrial and A-V nodal function; increases the refractory period of A-V node and ventricles; and slows the conduction in A-V node and specialized conducting tissues. Its hemodynamic effects include bradycardia, increase in cardiac output and a fall in peripheral and coronary vascular resistance. It can be used orally and intravenously. It has a wide spectrum of adverse

effects which include anorexia, nausea, abdominal pain, tremor, hallucinations, peripheral neuropathy, visual disturbances, elevation of plasma SGPT, hypotension, A-V block, hypersensitivity pneumonitis and asymptomatic corneal microdeposits.

The drug is used to treat life threatening arrhythmias not responding to other drugs.

Aprinidine, like amiodarone, is useful in controlling refractory ventricular (and, to a smaller extent, supraventricular) tachyarrhythmias, its electrophysiological effects resemble

Table 25.2 : Drug Treatment of Cardiac Arrhythmias

Arrhythmia	Emergency Treatment		Chronic treatment and prophylaxis
	Preferred treatment	Other treatment	
S.A. Node :			
Sinus arrhythmia	Needs no treatment	-	
Sinus tachycardia	Sedative, Propranolol	Treat the cause	-
Sinus bradycardia	Atropine	Treat the cause	-
Atria			
Premature beats	Sedative, Propranolol	Quinidine, Procainamide, Disopyramide	Quinidine, Procainamide, Disopyramide, Digitalis*
Paroxysmal tachycardia (P.A.T.)	Vagal manoeuvres, I.V. Verapamil	Digitalis I.V. Propranolol	Quinidine, Disopyramide, Procainamide, Propranolol, Digitalis*
P.A.T. with hemodynamic compromise	D.C. cardioversion		Quinidine
Atrial fibrillation	To control ventricular rate : Digitalis, Propranolol,	To terminate fibrillation : a) Digitalis + Quinidine b) D. C. cardioversion	Digitalis, Propranolol, Quinidine
Atrial Flutter	Same as for atrial fibrillation	Same as for atrial fibrillation	Same as for atrial fibrillation
Ventricles :			
Premature beats	Lignocaine, I.V. Procainamide	Quinidine, oral Procainamide, Disopyramide.	Quinidine, Procainamide, Disopyramide, Digitalis*, Propranolol**
Paroxysmal tachycardia (P.V.T.)	Same as above	Same as above	Same as above
P.V.T. with haemodynamic compromise	D.C. cardioversion		Quinidine
Ventricular fibrillation	Defibrillation	Lignocaine, I.V. Bretylium	Quinidine, Procainamide, Disopyramide.
Digitalis induced tachyarrhythmias	Lignocaine	I.V. Phenytoin	
Complete A. V. Block	Atropine	Isoprenaline	Pacemaker

* = If related to congestive cardiac failure, ** = useful when ventricular tachyarrhythmias are associated, with increased sympathetic tone or circulating catecholamines.

those of quinidine. It is under evaluation.

BRETYLIUM: This drug is an adrenergic neurone blocker and also appears to have direct actions on myocardium. Orally it has variable absorption; hence usually it is given I.V. or I.M. The main use of bretylium is in the treatment of ventricular tachycardia and ventricular fibrillation resistant to other nodes of treatment.

DRUGS USED IN THE TREATMENT OF HEART-BLOCK

ISOPRENALINE (Isoproterenol): The effects of isoproterenol in enhancing the rhythmicity of sinus as well as subsidiary nodal and ventricular pacemakers have proved invaluable in the treatment of advanced second degree and high grade A-V block. In emergency, the drug is administered intravenously in the dose of 2 mg. in 500 ml. of 5 per cent dextrose under electrocardiographic control. In less urgent situations, it is generally given sublingually in the dose of 10-15 mg. every 4-6 hours. Isoproterenol has also proved effective in abolishing ventricular tachycardia in the presence of advanced atrioventricular block. Isoproterenol acts by:

(a) acceleration of the basic sinoauricular pacemaker resulting in the suppression of ectopic ventricular activity,

(b) enhancing A-V conduction; and

(c) an increase in the cardiac output as a result of increased heart rate. This tends to augment the coronary flow.

Other sympathomimetic drugs like adrenaline and ephedrine are less effective than isoproterenol.

Corticosteroids are helpful when the heart block is due to an inflammatory disorder such as rheumatic fever. Injection of atropine is also useful in treating this condition.

Arrhythmias associated with hypotension as in acute myocardial infarction may be corrected by restoration of blood pressure using vasopressor drugs like noradrenaline.

Electrical depolarization of the heart: Termination of arrhythmias has also been achieved by the use of AC and DC depolarization. The latter procedure is safer.

Arrhythmias are precipitated by asynchronous discharge of contiguous myocardial fibres. The resultant potential difference between these fibres allows previously discharged fibres to be reexcited and this leads to perpetuation of the arrhythmia. Simultaneous depolarization of all the fibres eliminates asynchrony by ensuring synchronous repolarization and the dominant pacemaker (S.A. node) reassumes the control of the heart.

Electroversion has been used successfully in supraventricular tachycardias (atrial fibrillation, flutter and paroxysmal atrial tachycardia). It is a life-saving procedure in case of ventricular tachycardia and fibrillation. However, electrical cardioversion does not obviate the need for antiarrhythmic drugs which must be used to prevent the recurrence of the arrhythmias.

It is contraindicated in digitalis induced arrhythmias. When it is used for treating other types of arrhythmias, digitalis is generally omitted for 24 hours before electroversion. It may induce ventricular fibrillation if employed during advanced A-V block.

DC shock is used under intravenous diazepam cover.

REQUIREMENTS OF AN IDEAL ANTIARRHYTHMIC DRUG

- An ideal antiarrhythmic agent should be
- (1) effective against a specific group of arrhythmias;
 - (2) have no adverse effects, particularly cardiac ones;
 - (3) be effective orally as well as intravenously;
 - (4) long acting;
 - (5) produce stable plasma levels so that monitoring of drug level is not necessary; and
 - (6) Cheap and easily available.

26 Pharmacotherapy of Hypertension

Hypertension as a clinical entity has been divided into two major divisions according to etiology; *primary or essential hypertension*, where definite cause for the rise in blood pressure is not known and *secondary hypertension*, secondary to renal (chronic diffuse glomerulonephritis, pyelonephritis, polycystic kidneys), endocrine (Cushing's syndrome, pheochromocytoma, primary hyperaldosteronism) and vascular (renal artery disease, coarctation of aorta) lesions.

The syndrome of essential hypertension is characterised by elevation of the *diastolic blood pressure*, a normal cardiac output (in most cases) and increased peripheral vascular resistance, with documented natural history and with characteristic pathologic changes in the arterioles. The World Health Organization has defined 'hypertension' as a state in which systolic pressure is 150 mm. Hg. or more and diastolic pressure is 95 mm. Hg. or more.

In adults, the normal casual blood pressure varies according to age. Thus

- (i) upto 30 years it is 110-145 mm. systolic/
68-92 mm. diastolic.
- (ii) upto 45 years, it is 110-155 mm. systolic/
70-96 mm. diastolic.
- (iii) upto 60 years, it is 115-170 mm. systolic/
70-100 mm. diastolic.

If the W.H.O. definition of hypertension is strictly applied, 1/3rd of the men and 2/5ths of the women over 40 years of age and majority of men over 60 and women over 50 probably have hypertension. It is, however, a moot point whether all such cases should be subjected to treatment with drugs. It is usually agreed that people with diastolic pressure of 100 mm. Hg. or more deserve investigations and a trial with drug therapy.

Hypertension, if left untreated, leads to a variety of disabling cardiac, cerebrovascular,

and renal complications, with shortened expectancy of life. These complications and early deaths occur regardless of the etiology of hypertension. Further, the risk of morbidity and mortality rises with blood pressure and there is no clearly defined cut-off point for increased risk.

The etiology of primary hypertension is not clear but certain factors are implicated in its genesis:

(a) The work of Platt, Morrison and Morris has shown that the rise in blood pressure with age in a population as a whole is not uniform, but is due to the development of hypertension in a discrete group of individuals with advancement of age. These individuals, therefore, are presumed to differ qualitatively from the remainder of the population in their blood pressure regulation. The inheritance of essential hypertension is polygenic in nature.

(b) The arterial pressure is a function of the cardiac output and the peripheral resistance. Both these can be readily affected by various factors. Resistance to the blood flow chiefly resides in the arteriolar segment and about two-thirds of the arterial pressure head is used up in forcing blood past the arterioles. Relative to arterioles, the resistance offered by the arteries, veins and capillaries is very small. Changes in the calibre of the arterioles, therefore, produce enormous changes in the peripheral resistance. Arterioles have very reactive smooth muscle in their walls, which can be acted upon by various factors. Factors which tend to diminish the radius of these blood vessels, therefore, will augment the total peripheral resistance and consequently, the blood pressure.

(c) Normally, the blood pressure is controlled by two main types of systems. The one operates through the baroreceptors and the autonomic nervous system and is mainly responsible for the counteracting acute changes in the blood pres-

sure. Baro-receptor reflexes protect the circulation against stresses which would tend to alter arterial pressure acutely. When one stands up from the lying down position the cardiac output tends to fall due to reduced venous return to the heart. This may lead to a fall in blood pressure and fainting. Normally, this tendency to a fall in blood pressure is prevented by a rapid reflex increase in heart rate and in peripheral resistance through the baroreceptor mechanism.

In hypertensive individuals, increase in the sodium concentration of the vessel wall has been reported. In addition, the ability of the vessel wall to bind noradrenaline is found to be decreased resulting in less bound and more free noradrenaline. Both these factors tend to augment the total peripheral resistance by increasing vasoconstriction.

The second system, a humoral system, has a slow response and is probably important in long term regulation of arterial pressure. This system, which operates through the kidneys and involves various humoral agents, is known as the renin-angiotensin system. This system is increasingly incriminated particularly in the genesis of rapidly progressing hypertension (Fig. 26.1).

It has been demonstrated that reduction in blood flow to the kidney results in the elaboration of the enzyme renin, probably by the juxtaglomerular cells. The reaction between renin and a serum globulin (angiotensinogen, a renin substrate) results in the synthesis of an inactive decapeptide, 'angiotension I' which during its passage through the lungs is converted into an octapeptide, 'angiotension II' by the action of another enzyme. Angiotensin II is the most powerful direct vasoconstrictor agent, effective in as small a dose as 0.1 µg per kg. body weight. The role of angiotension in the genesis of hypertension is not clear. Angiotensin II also stimulates the synthesis and release of aldosterone from the adrenal cortex and is thus concerned in regulation of the E.C.F. volume. Many hypertensives do not have abnormally high plasma concentrations of angiotensin while even some normotensive individuals may show raised plasma level of angio-

tensin. Angiotensin II is converted into a heptapeptide Angiotensin III which is as potent as angiotensin II in its action on the adrenal cortex but is weaker in its other actions. "The kidney thus plays an important role in determining the blood pressure level, doing so via renin aldosterone system activity, which presides over both vasoconstriction and volume, the two major determinants of blood pressure and of tissue flow".

In man, many procedures that increase sympathetic nervous activity are associated with increased plasma renin activity (PRA). It is claimed that morbidity in the hypertensives is related to PRA. Whereas the adrenergic-blocking drugs, methyldopa, reserpine and propranolol reduce PRA, vasodilator antihypertensives such as hydralazine, diazoxide, sodium nitroprusside and the thiazide diuretics increase PRA in hypertensive patients.

(d) Page has advanced the concept that hypertension is a disturbance of homeostasis in which the baroreceptor control mechanism is set at a higher level than in the normal individuals. This baroreceptor mechanism can be 'reset' to original normal levels following drug therapy.

(e) It has been shown that some patients with labile hypertension and mild essential hypertension have tachycardia and increased cardiac output but normal peripheral resistance. These findings are indicative of a hyperkinetic circulatory state due to increased beta adrenergic activity. These patients also have elevated PRA (HREH, High Renin Essential Hypertension). Some other patients with essential hypertension have either normal or even low PRA (LREH, Low Renin Essential Hypertension). By contrast, majority of patients with essential hypertension have normal PRA.

Experimental evaluation of antihypertensive drugs: Although many technics have been devised for causing a sustained rise in the blood pressure in various species, none has duplicated, in every detail, the picture of human essential hypertension. The important experimental models for evaluating antihypertensive drugs are:

(i) **Nephrogenic hypertension:** (a) Dogs can be made hypertensive by partial constriction of one renal artery, accompanied by removal of the other kidney (Goldblatt). (b) Similar hypertension can be produced in the rat without removing the other kidney.

(ii) **Neurogenic hypertension:** (a) Sectioning of the carotid sinus and the aortic arch nerves produces hypertension in dogs. (b) Other methods of producing neurogenic hypertension include subjecting rats to intermittent loud noise and injection of kaolin into the cisterna magna of dogs.

(iii) **Hormonal hypertension:** The methods used include (a) Prolonged administration of deoxycorticosterone acetate (DCA) or aldosterone with sodium chloride in chicks and rats. (b) Severe hypertension can be produced in uninephrectomized and uniadrenalectomized, salt treated rats during regeneration of the enucleated adrenal cortex.

(iv) Ingestion of salt is necessary for the development of hypertension in many models of hypertension in animals.

(v) Finally, spontaneously hypertensive rats (SHR) are available. They would seem to come closest to human essential hypertension.

Drugs like methyldopa and beta blockers have little hypotensive effect in animals; but they are found highly effective in hypertensive human subjects. Hence, the final evaluation should be in hypertensive human subjects. Such studies generally include: (i) The timecourse relationship of the hypotensive effect. (ii) The dose-response relationship. (iii) The observation of adverse effects and drug interactions and, (iv) Haemodynamic studies during such therapy.

The drugs used in the treatment of hypertension act by reducing the cardiac output and/or reducing the total peripheral resistance, without correcting the cause. They can be classified according to site of action as follows (Fig. 26.1).

I. Drugs acting centrally: Clonidine and Methyldopa.

II. Drugs acting on the autonomic ganglia: Ganglion blocking agents--

(a) Quaternary ammonium compounds: Hexamethonium, Pentolinium, Chlorisondamine.

(b) Secondary amines: Mecamylamine.

(c) Tertiary amines: Pempidine and Trimethaphan.

III. Drugs acting on the postganglionic sympathetic nerve endings:

(a) Adrenergic neurone blockers: Guanethi-

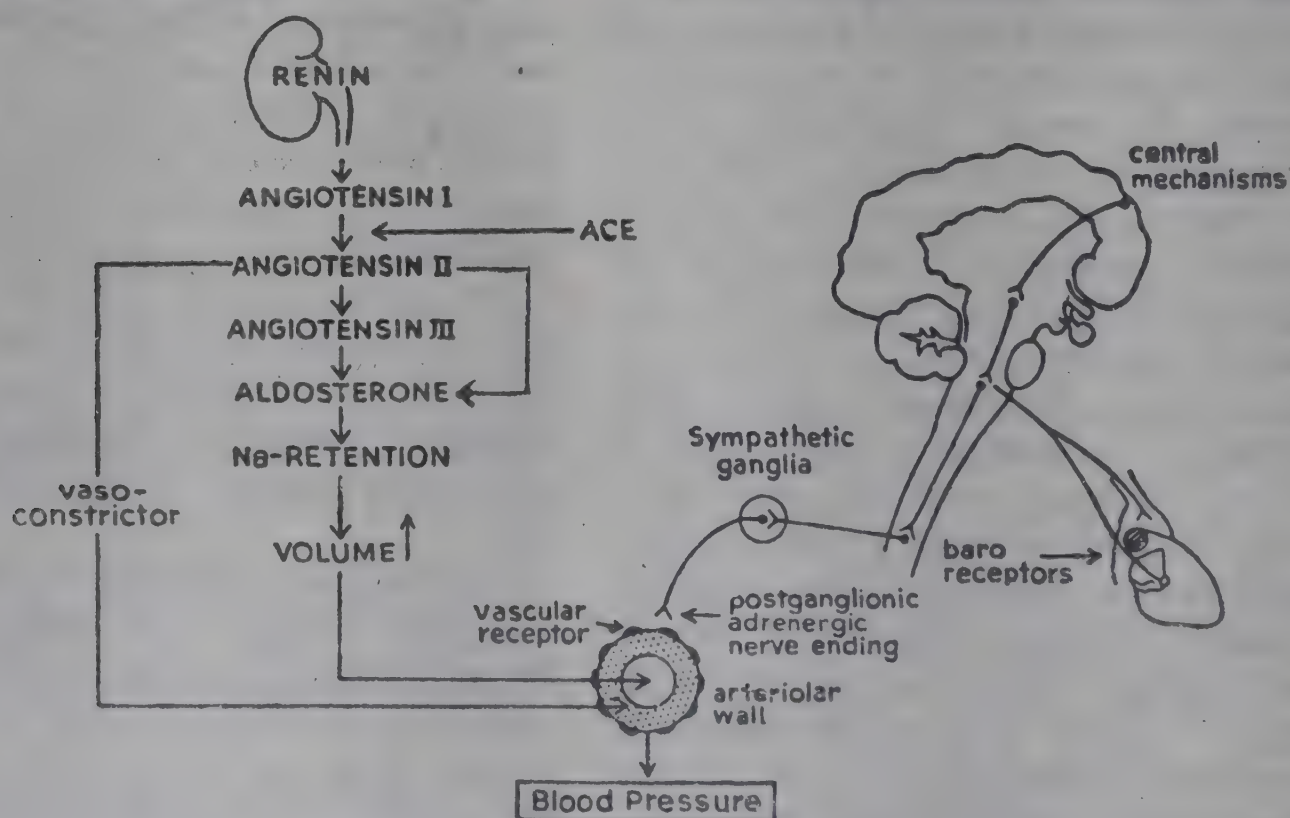


Fig. 26.1 : Site of action of hypotensive drugs.

dine, Bethanidine, Debrisoquine, Bretylium.

(b) Catecholamine depletors: Reserpine.

IV. Drugs acting on adrenergic receptors:

(a) Alpha-adrenergic blocking agents: Phentolamine, Phenoxybenzamine, Prazosin, Indoramin.

(b) Beta-adrenergic blocking agents: Propranolol.

(c) Both alpha and beta adrenergic blocking drugs: Labetalol

V. Drugs acting directly on the vascular smooth muscle (Vasodilators):

(a) Arteriolar vasodilators: Hydrallazine, Diazoxide, Minoxidil, Calcium channel blockers.

(b) Arteriolar-venular vasodilators: Sodium nitroprusside.

VI. Drugs acting reflexly by stimulating baroreceptors: Veratrum.

VII. Drugs which block renin-angiotensin-aldosterone axis:

(a) Those which block renin release: Beta-adrenergic blockers.

(b) Those which block the conversion of angiotensin I to angiotensin II by inhibiting the angiotensin converting enzyme (ACE): Captopril, Enalapril.

(c) Those which competitively block angiotensin II at the vascular receptor sites: Saralasin.

(d) Those which counteract the action of aldosterone: Spironolactone.

VIII. Oral diuretics: Thiazides.

IX. Miscellaneous: MAO inhibitor Pargyline, Metyrosine.

It must be emphasized that various antihypertensive compounds may ultimately reduce blood pressure in humans by more than one mechanism. Further, it has also been demonstrated that the hemodynaemic alterations produced by a single parenteral dose of a given drug may differ from the effects resulting from its prolonged oral administration. Moreover, the degree of hypotensive effect produced also differs in hypertensive and normotensive subjects.

I. Drugs acting centrally:

CLONIDINE (Catapres, Arkamin): This

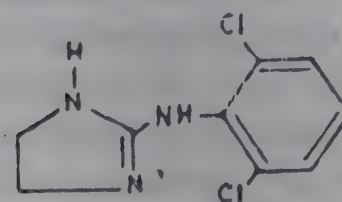


Fig. 26. 2: Clonidine

imidazoline derivative is a potent antihypertensive drug.

Pharmacological actions: Given intravenously in normal and hypertensive man, it produces a short hypertensive response followed by a prolonged reduction in both systolic and diastolic blood pressure accompanied by bradycardia. Such initial hypertensive effect is not seen after its oral administration. The rise in blood pressure is blocked by α -adrenergic receptor blocking drugs (phentolamine and tolazoline). Chronic administration, 0.3 to 1.5 mg/day reduces both supine and standing blood pressure in hypertensive patients. Baroreceptor reflex activity is relatively normal and circulatory reflexes are intact; hence, postural hypotension is not much of a problem during clonidine therapy. Its major action is due to stimulation of central α_2 -adrenergic receptors though there is a peripheral element as well. Alpha₂-adrenergic receptors are now known to exist in the vasomotor centre and hypothalamus. Their stimulation by clonidine blocks the release of noradrenaline from the nerve terminals, leading to lowering of blood pressure and bradycardia, and to increase in the activity of the peripheral vagal, cholinergic nerve endings. Peripherally, clonidine stimulates inhibitory presynaptic alpha₂ receptors, thus impairing the adrenergic neurotransmission. Peripheral stimulation of alpha₁-receptors causes vasoconstriction. This however, is not evident with therapeutic oral doses. Clonidine reduces the PRA. It also produces sedation and many symptoms of behavioral depression in laboratory animals. Almost all the central effects of clonidine can be blocked by the alpha₂ blocker yohimbine.

Clinical studies indicate that clonidine, given

alone, has a modest antihypertensive action. Addition of a diuretic potentiates its effect. It causes a decrease in the cardiac output due to both a decrease in stroke volume and bradycardia. In addition, it causes significant reduction in the total peripheral resistance in standing position. The muscle blood flow is not much affected while the renal blood flow is maintained during the hypotensive response; this is an advantage. Tolerance to antihypertensive effect develops on prolonged use. Since alpha adrenoreceptors are widely distributed, their interaction with clonidine can produce other effects such as decrease in insulin secretion and increase in the level of plasma growth hormone.

Absorption, fate and excretion: It is a lipid soluble drug, is well absorbed from the gut and has a high volume of distribution. Its plasma half life is about 12 hours and hence, two doses per day would be sufficient in therapy. About one half of the drug is excreted unchanged in the urine.

Preparations: Clonidine is available as 0.1 mg. tablets.

Adverse reactions: It causes drowsiness (central sedative action) and dryness of mouth due to central inhibition of salivation in large number of patients; vertigo, constipation, parotid pain, impotence, gastrointestinal disturbances and allergic reactions can also occur. Rarely, hallucinations can occur. Orthostatic symptoms, however, are uncommon. Tricyclic antidepressants like desipramine may impair the hypotensive action of clonidine. Clonidine potentiates insulin-induced hypoglycemia in man. Toxic doses cause marked bradycardia, miosis and hypotension.

Combination of clonidine and a betablocker can cause severe drowsiness. Abrupt cessation of clonidine therapy can cause hyperirritability and a dangerous and often lethal rebound rise of blood pressure. The treatment of this rebound hypertension is either re-institution of clonidine or a combination of an alpha and a beta adrenergic blocking agent. When clonidine must be

withdrawn, gradual tapering is preferable. If elective surgery is planned, substitution of another antihypertensive drug is advisable. Clonidine produces refractory sodium retention and, therefore, rapid development of tolerance to its antihypertensive effect unless it is combined with a diuretic.

Therapeutic Uses:

(i) **Hypertension:** See later.

(ii) **Migraine:** Clonidine hydrochloride administered orally in the dose of 0.025 mg twice daily appears to be prophylactically useful in about 70 per cent of migraine patients. The drug is more effective in those in whom the attacks are associated with particular foods such as chocolate, cheese, alcohol, and citrus food. The mechanism of action is unknown. The maximum total daily dose recommended for normotensive patient is 0.15 mg. Larger doses may cause hypotension. It is, however, better to avoid the drug in patients with history of depressive illness.

(iii) The drug has also been reported to be useful in glaucoma, in the management of opiate withdrawal syndrome and in menopausal hot flushes.

(iv) It has been successfully used in some children with retarded growth due to defective release of growth hormone from the anterior pituitary, consequent to hypothalamic dysfunction.

Guanfacine is related to clonidine and has actions similar to clonidine. Duration of action, however, is prolonged.

ALPHA METHYLDOPA (Aldomet, Em-dopa): The isomer of methyldopa which bears a close similarity to dihydroxyphenylalanine (DOPA) was introduced in the treatment of hypertension in 1960 by Sjoerdesma. It is effective by mouth and is used widely in the treatment of moderate to severe hypertension.

Pharmacological actions: After oral or intravenous administration, the hypotensive effect appears after a latent period of 3 to 6 hours and 1-2 hours respectively. It also decreases the heart

rate. The fall in blood pressure is more in hypertensive than in normotensive subjects, and in standing than in supine position. The hypotensive effect is associated with a reduction in cardiac output, total peripheral resistance or both. With time, this reduction in output seems to be less apparent. The drug does not interfere with the normal responses to nerve stimulation and does not abolish the cardiovascular reflexes. Postural hypotension, therefore, occurs less frequently with this drug than with guanethidine and the drug, unlike guanethidine, does not reduce the renal blood flow and glomerular filtration. Hence, it is especially valuable in patients with compromised renal function. Its hypotensive effect is enhanced by simultaneous use of thiazides.

The mechanism of action of methyldopa is not established with certainty. The current evidence suggests that alpha-methyl noradrenaline, a metabolite of methyldopa, acts centrally by stimulating the α_2 -adrenergic receptors in the vasomotor centre; thus, the action of methyldopa is similar to that of clonidine. Moreover, methyldopa inhibits renin release by the kidneys, though the contribution of this to the antihypertensive effect is not clear.

Methyldopa increases serum prolactin levels.

Absorption, fate and excretion: On oral administration, 50 per cent of the drug is absorbed. Peak effects are produced after 2 to 4 hours. The drug is almost completely excreted in urine in 12 hours. In patients with severely impaired renal function, the drug may accumulate during chronic administration.

Adverse reactions: Commonly it produces sedation, headache and fatigue. These usually tend to disappear with continuation of therapy. In certain cases, however, these may reappear after increasing the dose of the drug and necessitate cessation of drug treatment. Other effects referable to the central nervous system are diminished intellectual drive, drowsiness, forgetfulness, changes in sleep rhythm, nightmares, lactation in females, mental depression and parkinsonism. Tolerance to the antihypertensive effect is com-

mon, particularly during the initial few weeks of therapy. Postural hypotension is a rare occurrence with alpha methyldopa. The drug has also been reported to cause retention of sodium and water.

Alpha methyldopa produces fever accompanied by alteration in the liver function tests and either parenchymal or cholestatic jaundice in a few cases. Rarely it causes thrombocytopenia and agranulocytosis.

G.I. upset, constipation, nasal congestion, failure of ejaculation, arthralgia and skin rashes are rarely encountered with this compound. The compound and its metabolites interfere with the measurement of urinary catecholamines by fluorometry.

Preparations: Alpha methyldopa (Aldomet, Emdopa) 250 mg. tablets.

Alpha methyldopa hydrochloride injection in 5 ml vials containing 50 mg. per ml.

II. The ganglionic blocking agents:

The ganglion blocking drugs were initially used on a large scale in the treatment of hypertension. However, the high incidence of adverse effects, development of tolerance, unpredictable absorption from the gut and the advent of safer and equally potent hypotensive agents reduced considerably their application in therapy.

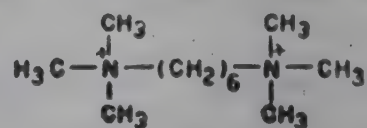


Fig. 26.3 : Quaternary ammonium compound
Hexanethonium

Pharmacological actions: The ganglion blocking agents block the transmission of impulses in the sympathetic and the parasympathetic autonomic ganglia without modifying the conduction of impulses in the preganglionic or post-ganglionic neurones. They produce ganglionic blockade by occupying receptor sites on the ganglion cells. Ganglion blockade of transmission results in reduction in the amount of noradrenaline release from the post-ganglionic

sympathetic nerve endings and thus induces a reduction in the peripheral sympathetic tone and a fall in blood pressure. The normal protective vasomotor reflexes mediated through the baroreceptors and the sympathetic nervous system are also blocked and hence, the hypotensive effect is more marked in standing than in supine posture; this results in marked postural hypotension.

The ganglion blocking agents reduce the cardiac output by reducing the venous return as a result of venous dilatation and peripheral pooling of blood.

The ganglion blocking agents enhance the sensitivity of the patient to sympathomimetic amines and these (noradrenaline) should be used cautiously and in reduced dosage when treating severe hypotension induced by ganglion blocking agents.

Absorption, fate and excretion: The absorption of the quaternary ammonium compounds from the gut is incomplete and unpredictable. In contrast, tertiary amines like mecamylamine and pempidine are better absorbed orally.

After absorption, the quaternary ammonium compounds are confined to the extracellular space and do not cross the blood-brain barrier. They are excreted almost unchanged by the kidneys.

Mecamylamine and pempidine, on the other hand, penetrate into the cell. They also cross the blood-brain barrier, and are excreted unchanged by the kidney.

Adverse reactions: The ganglion blocking agents produce various adverse effects:

(a) *Parasympathetic blockade* results in visual disturbances such as mydriasis, cycloplegia and consequent blurring of vision, dryness of mouth, constipation, paralytic ileus and urinary retention. These can be counteracted by parasympathomimetic drugs like neostigmine.

(b) *Sympathetic blockade* results in marked orthostatic hypotension and disturbances in sexual function in males. Syncope is a troublesome and dangerous adverse effect.

(c) *Central actions:* The secondary and the tertiary amines, mecamylamine and pempidine,

may produce mental confusion, tremors, seizures, mania or depression.

(d) *Tolerance:* Development of tolerance including cross tolerance with other ganglion blocking agents, except mecamylamine, is a major drawback.

(e) *Miscellaneous:* Trimethaphan camphor sulfonate may produce anuria, vascular thrombosis and shock on intravenous administration. It should be avoided in allergic individuals.

Preparations: Oral ganglion blocking drugs are now rarely used because of their toxicity and availability of better drugs.

Trimethaphan camphor sulfonate (Arfonad): Because of its extremely transient action, this compound is used only for production of controlled hypotension for short periods, during surgery. Each ampoule contains 0.25 g. of sterile powder of trimethaphan camphor sulfonate. It is administered by intravenous infusion as 1 mg./ml. solution. The rate of the infusion is controlled to maintain the desired level of hypotension.

III. Drugs acting on the post ganglionic sympathetic nerve endings:

(a) **Adrenergic neurone blocking agents** are the drugs that, without depleting the neurotransmitter, act on the post-ganglionic sympathetic neurones to inhibit the ability of a nerve impulse to release noradrenaline. The ganglionic transmission is unaffected and the effector organs are fully responsive to injected noradrenaline. These drugs probably act, therefore, on the sympathetic nerve terminals, where they prevent the release of the transmitter. Their action is selective in that they do not block the parasympathetic nervous system. Since these drugs do not cross the blood-brain barrier easily their actions are mainly peripheral. In higher concentrations they may inhibit the 'adrenergic membrane pump'.

Bretylium tosylate was synthesized in 1959 by Boura and Green and was the first adrenergic neurone blocking agent to undergo a therapeutic trial. Although the preliminary results were encouraging tolerance to the drug develops in approximately 60 per cent individuals within 4

months. Currently used adrenergic neurone blockers are:

GUANETHIDINE (Ismelin) was synthesized in 1961 by Maxwell, Mull and Plummer. It is employed in the treatment of moderate or severe hypertension, given alone or in conjunction with other hypotensive agents. Development of tolerance is not a major problem with guanethidine.

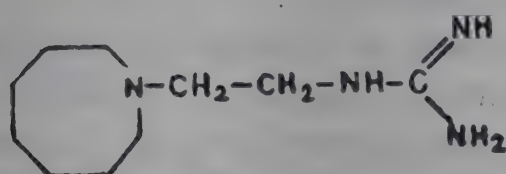


Fig. 26.4 : Guanethidine.

Pharmacological actions: The antihypertensive effect of guanethidine is usually delayed for 48 to 72 hours following oral administration, however, the ensuing blood pressure reduction is generally prolonged for seven or more days, once an effective response has been obtained. The fall in blood pressure is more marked in hypertensive than in normotensive individuals. Guanethidine abolishes the protective cardiovascular reflexes mediated via the sympathetic nervous system and the carotid baroreceptors, and may thus produce postural hypotension. Cardiovascular and pressor responses to exercise are impaired and cold pressor response is reduced. It does not suppress but rather augments the pressor responses to adrenaline and noradrenaline. The reduction in blood pressure achieved by guanethidine is attributed mainly to a reduction in the cardiac output as a result of venous pooling. The heart rate is usually decreased and the pulse pressure is reduced.

On intravenous administration, guanethidine exerts a transient sympathomimetic action before producing a fall in blood pressure. This is accompanied by an increase in the heart rate.

The exact mechanism of the hypotensive action of guanethidine is not clear. Because of its low lipid solubility, guanethidine does not cross the blood-brain barrier and hence its hypotensive effect is probably entirely peripheral. After

administration the drug is selectively taken up by adrenergic neurone, the uptake mechanism being similar to uptake of noradrenaline. The adrenergic neurone blockade produced by guanethidine is a result of :

(a) Inhibition of the release of the transmitter noradrenaline at the sympathetic nerve terminals. The pressor effect of tyramine is still maintained.

(b) Blockade of re-uptake of noradrenaline by the sympathetic nerve endings, observed following higher doses (Fig. 26.5). This effect may also account for the transient sympathomimetic activity of guanethidine observed on intravenous administration.

(c) Depletion of noradrenaline stores at the sympathetic nerve endings and tissues such as the heart, the aorta and the spleen. Depletion is a relatively slow process and may not account for the rapid onset of the blockade in therapeutic doses. Another adrenergic neurone blocker debrisoquine does not deplete tissue catecholamines.

Chronic treatment with adrenergic neurone blockers has been shown to cause histological damage to adrenergic nerve structures in experimental animals.

Absorption, fate and excretion: Guanethidine is incompletely absorbed from the gastrointestinal tract. Twenty per cent of the absorbed drug is excreted in urine in 24 hours and 36 per cent in 72 hours; on intravenous administration, 50 per cent of the drug is eliminated in urine within 24 hours. The drug accumulates in the body on prolonged administration and cumulative toxicity may occur.

Adverse reactions: Most of the adverse effects of guanethidine can be explained by its blockade of sympathetic function. The most important complication is postural hypotension. It is usually observed in the morning and is accentuated by exercise. *This may be accompanied by relatively higher blood-pressure in the evening. The physician should be aware of this possibility while increasing the dose of guanethidine.* Guanethidine should be used with great care in patient with diminished coronary, cere-

bral or renal blood flow. The drug has been demonstrated to depress the renal blood flow and G.F.R. In addition, guanethidine has been reported to produce failure of ejaculation, nasal congestion, nausea, vomiting and parotid tenderness. Diarrhoea is occasionally troublesome, but can be controlled by small doses of anticholinergic agents or binding mixtures. Fluid retention may occur and this might precipitate congestive cardiac failure. Tricyclic antidepressants inhibit the entry of guanethidine into the adrenergic neurone and can antagonize its antihypertensive action.

The use of guanethidine is contraindicated in pheochromocytoma as the sensitivity to pressor effects of adrenaline and noradrenaline is increased by guanethidine and it releases these catecholamines from the tumour. Guanethidine can produce mental depression despite its negligible penetration into the central nervous system. A few cases of polyarteritis nodosa following prolonged guanethidine therapy have been described.

Preparations: Guanethidine sulfate 10 mg. and 25 mg. tablet.

BETHANIDINE (Esbatal): This compound is closely related to guanethidine. It is relatively quickly absorbed and completely excreted in urine within 24 hours and hence, the hypotensive action is rapid in onset and short lived. Adverse effects are similar to those seen with guanethidine. The oral dose is 5 mg. 3-4 times daily, after food, increased by 5 mg. upto a maximum of 200 mg/day.

DEBRISOQUINE SULFATE (Declinax): This adrenergic neurone blocking agent, unlike guanethidine, does not deplete the tissue catecholamines. Given orally, it produces a fall in blood pressure, mainly by reduction in the cardiac output; the peak effect is achieved within 2 to 3 hours and the effect persists for 8 to 12 hours.

Debrisoquine is almost entirely excreted in urine. Therefore, the dosage has to be reduced in patients with impaired renal function.

The adverse effects are similar to those of guanethidine.

The drug is started initially in the dose of 10 mg. 2 or 3 times a day. The dose is increased by 10 mg. at 3 days intervals till a satisfactory control of blood pressure in the standing position is achieved. The usual maintenance dose lies between 40 to 120 mg. per day, though doses upto 400 mg. daily have been used. Tolerance may develop to this drug.

Guanoxon and Guanochlor, in addition to their adrenergic neurone activity, also block the alpha adrenergic receptors in the hypothalamus and the adrenal medulla. They do not offer any advantage over guanethidine.

(b) Catecholamine depletors:

RESERPINE: The root of the plant *Rauwolfia serpentina* has been in medicinal use in India since ancient times. It was considered useful for such diverse conditions as insomnia, snake bite and insanity. The root contains alkaloids reserpine, rescinnamine, deserpidine and ajmaline. Reserpine is by far the most potent of all hypotensive alkaloids whereas ajmaline has quinidine-like properties.

Pharmacological actions of reserpine: Reserpine, on oral or parenteral administration, produces its effects after an initial latent period. The hypotensive effect of the drug appears after 30 minutes on intravenous administration of a single dose, whereas given orally, the maximum effect develops as late as after 2 to 4 weeks of repeated medication. Hypotension is usually accompanied by bradycardia. Although there is a decrease in the peripheral resistance, reduction in the cardiac output as a cause of hypotension cannot be ruled out completely, particularly on chronic administration.

In therapeutic doses, reserpine probably does not block the homeostatic reflexes in man, but it acts synergistically with other hypotensive agents, particularly the diuretics and the ganglion blocking agents. Reserpine pretreatment enhances the pressor response to sympathomimetic amines like adrenaline and noradrenaline, and this fact must be kept in mind when the sympath-

omimetic amines are to be employed in individuals on reserpine therapy.

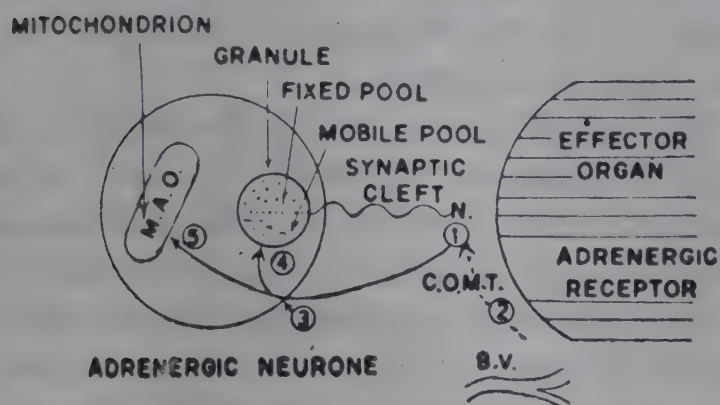


Fig. 26.5 : Mechanism of action of reserpine. For explanation please refer to the text.

The exact mechanism by which reserpine reduces blood pressure is not established. It is, however, known to deplete the catecholamines, adrenaline, noradrenaline and dopamine from the various storage sites in the body. This is accompanied by depletion of 5-hydroxytryptamine as well, particularly from the central nervous system. The depletion of noradrenaline stores in the peripheral sympathetic nerve endings including those of heart is a probable explanation for the hypotensive action of reserpine.

Normally, the endogenous noradrenaline located inside the chromaffin granules present in the sympathetic nerve endings is metabolised as follows:

(1) Sympathetic nerve stimulation releases noradrenaline from the mobile pool into the synaptic cleft.

(2) A part of the released noradrenaline is inactivated by specific enzyme catechol-O-methyl transferase (C.O.M.T.), while a part is carried away by the blood.

(3) A large portion of released noradrenaline is taken up by the sympathetic nerve endings. This reuptake is blocked by guanethidine in high doses but not by reserpine.

(4) A part of noradrenaline inside the nerve endings is taken up by the intracellular 'granules' or 'vesicles' existing in the adrenergic neurones and is subsequently stored in them. This stored

noradrenaline is released again into the synaptic cleft as a result of nerve stimulation.

Granular uptake of intraneuronal noradrenaline and its subsequent storage are two distinct but linked granular functions. Reserpine probably acts on both 'the granular uptake' and 'granular amine storage'. The former is competitive in nature and hence reversible while once the reserpine has interacted with the storage system the storage remains inhibited even in the presence of the amine. This causes granular noradrenaline depletion. Thus, reserpine initially acts reversibly and later irreversibly (Fig. 26.5).

(5) Part of the intracellular noradrenaline is destroyed by the non-specific enzyme monoamine oxidase (M.A.O.) located inside the mitochondria of the nerve cell.

(6) In addition, reserpine also inhibits the storage of freshly synthesized noradrenaline within the granules.

Thus, the reserpine action leads to depletion of the transmitter and consequently to peripheral sympathetic blockade. The transmitter which 'leaks out' from the storage granules is inactivated by the mitochondrial M.A.O. and the inactivated products are released from the sympathetic nerve endings. It is for this reason that reserpine does not exhibit any sympathomimetic activity; however, if the enzyme M.A.O. is inhibited by any M.A.O. inhibitor before, subsequent reserpine administration may produce a rise in blood pressure.

The drug also inhibits the release of renin.

Central nervous system: Reserpine has sedative and antipsychotic actions. (See Chapter 11).

Other pharmacological actions of reserpine include increased gastric acid secretion and augmentation of peristalsis. The drug has been used to induce experimental peptic ulceration in animals.

Absorption, fate and excretion: Reserpine is readily absorbed from the gastrointestinal tract and from the parenteral sites of injection. The drug appears to be rapidly taken up by lipid rich tissues and is distributed fairly uniformly in the various parts of the central nervous system. The

metabolic pathway of reserpine has not been definitely ascertained. The central and the peripheral effects of reserpine are established slowly and maintained for a long time even after complete elimination of the drug.

Adverse reactions: These usually develop as an extension of the pharmacological actions of reserpine. Excessive salivation, cutaneous vasodilatation, nasal congestion, increased motility of the gut and increased gastric acidity can be attributed to the peripheral sympathetic blockade or the parasympathetic dominance. Cutaneous vasodilatation may exacerbate dermatological disorders. Reserpine should be administered with caution in individuals with history of hyperacidity and/or peptic ulcer. Reserpine can prolong A-V conduction time, particularly if administered along with digitalis.

Orthostatic hypotension as a result of sympathetic blockade may occur; but except in patients with extensive cerebrovascular disease or otherwise defective vasomotor reflexes, it is infrequent. Reserpine must be used very cautiously in patients with recent stroke, since they may develop severe hypotension, drowsiness and even coma, particularly when the drug is given intramuscularly as in the management of hypertensive encephalopathy. Prior reserpine treatment has been reported to precipitate hypotension and death during induction of anaesthesia. Surgery should, therefore, be done in such patients with full access to resuscitative procedures.

The adverse reactions which develop as a result of central actions are as follows:

(i) Weight gain is due to an increased appetite and also due to retention of sodium and water. Frank congestive cardiac failure has been precipitated by reserpine therapy. Release of ADH by the central action of reserpine probably plays some part in water retention. The use of diuretics with reserpine reduces the danger of salt and water retention.

(ii) Mental depression is by far the most serious adverse effect of reserpine. It may assume serious proportions resulting in nightmares, insomnia and suicidal tendencies in some cases.

Hence, it is contraindicated in the presence of endogenous depression. Further, reserpine-induced depression lasts for a long time after stopping the drug and is resistant to treatment with tricyclic antidepressants. Reserpine may also exacerbate epilepsy.

(iii) Parkinsonism occurs following large doses of reserpine. However, this is reversible and can be easily controlled by antiparkinsonian drugs, though many prefer to stop reserpine.

(iv) Endocrine disturbances such as gynaecomastia and impotence in males and reduction in fertility in females have been reported with relatively large doses of reserpine.

Allergic manifestations are rare. These include thrombocytopenia and purpura.

Preparations and dosage: The important Rauwolfia preparations available for therapy are:

(1) Rauwolfia tablet, I.P., containing powdered root-bark standardised to contain 4 mg. of total alkaloids. The average daily dose is 2-4 mg.

(2) Reserpine tablet, I.P., containing 0.25 mg. of reserpine. The dose is 0.25 to 1 mg. daily.

(3) Reserpine injection (Serpasil), available in 2 and 10 ml. ampoules containing 2.5 mg. per ml. It can be administered by intramuscular or intravenous route.

IV. Alpha and beta adrenergic blocking agents:

(a) **Alpha adrenergic blocking agents:** Peripheral vascular alpha-receptors are of two types (1) postsynaptic α_1 receptors and (2) presynaptic α_2 -receptors, which are inhibitory in nature. Blockade of α_1 will cause fall in blood pressure. However, simultaneous blocking of α_2 would result in enhanced output of noradrenaline leading to tachycardia. The alpha adrenergic blocking agents like phentolamine are of relatively little value in the treatment of essential hypertension. Their use is associated with preponderance of the beta adrenergic activity, palpitation and tachycardia. The detailed pharmacological action of these agents are discussed in Chapter 14.

PHENTOLAMINE (Regitine): Phentolamine, the alpha adrenergic blocking agent with a short duration of action, is used in the diagnosis of pheochromocytoma, the tumour of adrenal medulla which secretes adrenaline and noradrenaline. Intravenous administration of 5 mg. of phentolamine mesylate produces a fall of blood pressure, 35 mm. systolic and 25 mm. diastolic, or greater, within 2 minutes in an individual with pheochromocytoma. It must be remembered that a similar degree of fall of blood pressure may occur in patients with essential hypertension who are on a sedative or an antihypertensive drug or who have concomitant renal failure. Phentolamine may also be administered intravenously in the dose of 2.5 to 10 mg. to prevent or treat severe hypertension due to release of catecholamines during operative removal of pheochromocytoma. It may also be used to treat the severe hypertension induced either by guanethidine/reserpine administration or by clonidine withdrawal.

PHENOXYBENZAMINE: This long acting alpha adrenergic blocking drug is used in the preoperative preparation of patients with pheochromocytoma. Its use controls hypertension and causes an expansion of plasma volume; intraoperative hypertensive episodes are prevented; if the latter occur, they are treated with 2-5 mg of phentolamine intravenously. It is also used for long term management of inoperable cases of pheochromocytoma, where it is combined with a beta-adrenergic blocker.

PRAZOSIN (Minipress): This quinazoline derivative is a peripheral vasodilator. Its action involves alpha₁ adrenergic receptor blockade. The drug is relatively ineffective in blocking presynaptic α_2 -receptors which are inhibitory. Prazosin, is thus, less likely to cause reflex tachycardia. Though it has a short plasma half life (2.5 - 4 hours), its antihypertensive effect lasts much longer (10 hours). It is effective in all grades of severity of hypertension but its main use is for the treatment of moderate and severe hypertension as an adjunct to other drugs such as

diuretics, beta-blockers and methyldopa. It controls both supine and standing blood pressure with minimum of postural hypotension. Prazosin does not seem to affect renal function, cardiac output or the renin-angiotensin axis. In contrast to the direct peripheral vasodilators (hydralazine, diazoxide and minoxidil), prazosin produces little or no tachycardia at rest. The adverse effects are giddiness, drowsiness, tiredness, weakness, nausea, diarrhoea, fluid retention, palpitation and nervousness. It is customary to begin therapy with 1 - 3 mg/day in divided doses. The first dose should be 0.5 mg or less as some patients have adverse reactions such as palpitation, dizziness and even collapse and loss of consciousness following the first dose. This is especially likely to occur in sodium depleted patients and in those taking other antihypertensive medications. The usual maintenance dose is 3 to 7.5 mg/day. It is also used to treat congestive heart failure (See Chapter 24).

INDORAMIN: This alpha adrenergic blocker lowers the blood pressure. However, it does not appear to have any advantage over the established drugs.

DIHYDROGENATED ERGOT ALKALOIDS (Hydergine): These are discussed in detail in Chapter 14.

Hydergine is a mixture of the dihydro derivatives of the three alkaloids of the ergotoxine group, namely ergocornine, ergocristine and ergocryptine. Hydergine is available as 0.5 mg. sublingual tablets and as ampoules for intramuscular or intravenous administration containing 0.3 mg. in 1 ml. Absorption from the sublingual route is erratic. Administration by any route may produce nausea, malaise, vomiting and bradycardia. The hypotensive action is unpredictable and sometimes the drug may produce vomiting even without much hypotensive effect. It is now rarely used in antihypertensive therapy.

(b) **Beta-adrenergic blocking agents:** Their detailed pharmacology is discussed in Chapter 14. Only their antihypertensive effects are dis-

cussed here.

Pharmacological actions: Beta-adrenergic blocking drugs reduce elevated blood pressure in hypertensive patients. All of them seem to be equal in their ability to control hypertension and if one drug fails to control the blood pressure in the maximally tolerated doses, a change to another one generally does not help. Both systolic and diastolic blood pressures are lowered, both in the supine and standing positions. There is no accompanying tachycardia and in fact tachycardia caused by a drug such as hydralazine is prevented by a beta-blocker. The height of blood pressure reached during stress-induced hypertension is lowered, a great advantage in therapeutics. They do not block baroreceptor mechanisms and postural hypotension is generally not a problem. The antihypertensive response is a function of adequate dosage.

Their exact mechanism of action is not known but their antihypertensive effect seems to correlate best with their β_1 blocking action. Peripheral resistance is lowered during chronic administration. These agents do have some central effect on catecholaminergic neurons. Reduction in cardiac output and lowering of plasma renin are variable. They also reduce the tyrosine hydroxylase and dopamine- β -hydroxylase activities in the peripheral sympathetic nervous system.

Absorption, fate and excretion: See Chapter 14 for details. The clinical hypotensive effect of a single dose lasts longer than the $t_{1/2}$ (2-5 hours) would suggest and hence, most of these drugs can be used on a twice a day basis. Longer acting drugs such as atenolol can be used on a once a day basis. The onset of antihypertensive effect is dose-related but generally takes 5-7 days to become manifest.

Adverse reactions: See Chapter 14 for details. In general, these drugs are well tolerated and cause minimal toxicity. Abrupt cessation of beta-blocker therapy can result in potentially dangerous rebound rise of blood pressure. Cardiac enlargement is a relative contraindication to the use of beta-blockers. Concurrent use of clo-

nidine and propranolol results in excessive drowsiness. Paradoxical hypertension has been reported with large doses of pindolol. In a patient with pheochromocytoma, the use of a beta-blocker can cause a dangerous rise of blood pressure unless it is combined with an alpha-blocker. Deterioration of renal function has been reported in occasional patients with established renal disease.

Preparations : See Chapter 14.

Therapeutic uses: Beta-blockers can be used in the treatment of all grades of severity of hypertension. In mild hypertension, a beta-blocker may be used alone or to supplement a diuretic drug; in moderate and severe hypertension, a beta-blocker is generally combined with a diuretic, with or without the addition of a vasodilator. Beta-blockers are expensive at present and the addition of a diuretic considerably reduces the cost of treatment. The effective dosage range of propranolol is 20-400 mg. per day in divided doses. Patients with chronic obstructive lung disease should be treated with cardioselective drugs such as atenolol, metoprolol.

(c) Alpha and beta adrenergic blocking agents :

LABETALOL (Normadate): For details see Chapter 14. It is given orally in the dose of 100 mg. twice daily and increased gradually upto 400 - 800 mg daily. For treating hypertensive emergencies it can be given i. v.

V. Drugs acting directly on smooth vascular muscle :

HYDRALLAZINE (Apresoline, Nepresol): Hydralazine was first synthesized and tested for antihistaminic activity. However, subsequent investigations demonstrated its hypotensive action instead of antihistaminic activity. The drug was almost discarded because of its adverse effects in early clinical trials, but has again revealed its usefulness in combination with other drugs.

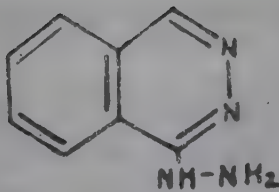


Fig. 26.6 : Hydrallazine.

Pharmacological actions: Hydrallazine lowers blood pressure in normotensive and hypertensive individuals. The effect is slow in onset but prolonged. Even on intravenous administration the blood pressure falls after a latent period of 15 to 20 minutes. The diastolic blood pressure is reduced more than the systolic blood pressure and this is accompanied by a decrease in the total peripheral resistance and an increase in the heart rate, the stroke volume and the cardiac output. Splanchnic, coronary, cerebral and renal blood flow is increased by hydrallazine unless the fall in blood pressure is very pronounced, and this is a probable advantage of this drug.

Hydrallazine acts by causing direct relaxation of the arteriolar wall. Prominent compensatory reactions to such vasodilatation include tachycardia, increased cardiac contractility, increased plasma renin activity and fluid retention.

Absorption, fate and excretion: Hydrallazine is well absorbed after oral and parenteral administration. Maximal blood levels are reached within 3 to 4 hours after oral administration and elimination of the drug is almost complete within 24 hours. Less than 5 per cent of an oral dose is excreted unchanged in urine. The drug may, therefore, be useful even in the presence of renal damage.

Although the plasma half life of this drug is short, its action is much longer because the drug becomes bound to vascular smooth muscle and twice daily regime is adequate. The drug is acetylated and there may be 'fast acetylators' and 'slow acetylators'.

Adverse reactions: The high incidence of toxic manifestations is the main drawback of hydrallazine therapy. The manifestations are :

(a) Cardiac effects: These include palpitations, tachycardia and anginal attacks.

(b) Gastrointestinal irritation producing nau-

sea, vomiting, gastric hypersecretion, possible activation of peptic ulcer, anorexia and diarrhoea. Other manifestations include headache, nasal congestion, flushing, tremors, dizziness, paresthesias, and conjunctivitis. The drug has also been reported to produce retention of salt and water and to cause acute psychotic episodes. Constipation and difficulty in micturition are other minor adverse effects for which the individual may develop tolerance on prolonged therapy.

(c) The drug may produce intolerance. The manifestations are fever, skin rash and polyneuritis. Gastrointestinal haemorrhage, anemia and pancytopenia are serious manifestations of drug intolerance and call for cessation of therapy.

(d) With heavy (over 600 mg. per day) and prolonged (over 6 months) dosage, a syndrome resembling acute rheumatoid arthritis or disseminated lupus erythematosus develops. Recovery occurs but often prolonged corticosteroid treatment is required and residual effects may persist in a few cases.

Preparations: Hydrallazine hydrochloride: tablets of 10, 25, and 50 mg. for oral administration. It is always used in combination with other drugs and the dose is not exceeded 200 mg. daily.

Dihydrallazine sulphate 25 mg. tablet (Nepresol).

Injection: available as 1 ml. ampoule containing 20 mg. of the drug. It can be administered by intramuscular or intravenous route.

DIAZOXIDE, is a compound structurally related to chlorothiazide. It is a potent vasodilator, acting directly on the arteriolar wall. As with hydrallazine, compensatory reactions include tachycardia, increased cardiac contractility and sodium retention. It has been used successfully in treating hypertensive emergencies. It is highly protein bound and must be injected intravenously (see later). It has also been used orally in the dose of 300-800 mg/day. Although effective, chronic administration is known to give rise to brittle diabetes, hirsutism, hyperuricemia and refrac-

tory fluid retention and hence needs strict supervision.

MINOXIDIL is a peripheral vasodilator drug used orally in the treatment of hypertension. Its actions are similar to those of hydralazine, but it is more potent and more toxic than the latter. There occur compensatory tachycardia, increased cardiac contractility and sodium retention. Combination with a beta-blocker is advisable to prevent tachycardia. It can also cause pulmonary hypertension, hypertrichosis and headache. Pericardial effusion and cardiac tamponade have been reported. Its effective dose range is wide, 5-40 mg/day. The drug is reserved for resistant cases.

Topical application of 1-3% minoxidil causes increase in dermal blood flow which may contribute to hair growth. It causes elongation of follicles in the area of alopecia. New follicles are not formed. Applied twice daily for many months, the drug may help to grow hair in about 25-30% of patients with alopecia. The onset of action takes 1-2 months, is unpredictable and the action disappears after stoppage of therapy.

SODIUM NITROPRUSSIDE : This drug is known since 1850 and has been used as a colour indicator for acetone and aldehydes. It was regarded as a poison because of its cyanide group. However, given in small doses, the drug has a specific, vascular-smooth-muscle relaxant action. Both arteriolar as well as venous smooth muscle are affected at equivalent doses, resulting in the reduction in peripheral resistance and venous tone, reducing the after load (impedance to left ventricular ejection) and the preload (left ventricular filling pressure) respectively. This results in reduced myocardial oxygen consumption and improved myocardial function in low output states. The fall in arterial pressure is accompanied by only minimal alteration in heart rate and other indices of cardiac function. The action is of rapid onset but of short duration. Hence, for continuous effect the drug is administered by intravenous drip. The patient should be

carefully monitored during sodium nitroprusside treatment.

Sodium nitroprusside is supplied as 50 mg powder to be dissolved in 500 ml of 5% dextrose in water, just prior to administration. Nitroprusside is light sensitive and a paper bag over the intravenous fluid container is necessary. Translucent plastic tubing may need taping. Only freshly prepared solutions should be used.

Adverse reactions: It may cause fatigue, anorexia, nausea, vomiting, sweating, disorientation, psychotic behaviour and muscle twitchings. Larger doses may cause rigidity and convulsions. The toxicity correlates with plasma levels of sodium thiocyanate to which sodium nitroprusside is metabolised; levels above 10 mg.% are dangerous.

Uses: Apart from its use in the emergency treatment of hypertension, nitroprusside has also been used to produce controlled hypotension during surgery and in acute myocardial infarction and other low output states to improve left ventricular function and cardiac output. It is given intravenously slowly in the dose of 1-4 µg/kg/min.

It may be emphasized that nitrates have a synergistic vasodilator effect with the above drugs and, therefore, the use of nitroglycerine by a patient receiving a peripheral vasodilator drug can lead to sudden fall of blood pressure and collapse.

CALCIUM CHANNEL BLOCKERS: Their properties are discussed in detail in Chapter 27. Verapamil and nifedipine are useful in the long term treatment of hypertension. Nifedipine has also been used in the management of hypertensive emergencies. Nifedipine is particularly useful in hypertensive emergencies in patients with impaired renal function and during pregnancy. Further, it may be preferred as a single drug in hypertensive patients with diabetes mellitus as it does not affect the secretion of glucoregulatory hormones.

VI. Drugs acting reflexly:

THE VERATRUM ALKALOIDS: The primary site of their action is the afferent receptors

predominantly in the heart and in the carotid sinus area. As a result of the sensitization of the afferent receptors, the peripheral sympathetic tone is reduced, producing hypotension. At the same time, the vagal tone is also increased and this induces bradycardia. (For details see earlier editions).

VII. Renin-Angiotensin antagonists:

SARALASIN: This synthetic analogue of angiotensin II is a competitive inhibitor of angiotensin II at vascular receptor site; however, it has significant partial agonist properties. When infused intravenously, it lowers the blood pressure in patients with angiotensin dependent hypertension (renovascular hypertension and malignant hypertension). The drug is used as a diagnostic agent.

CAPTOPRIL: This orally effective inhibitor of angiotensin converting enzyme (ACE) is D-3-mercapto-2-methyl propanoyl-L-proline.

Pharmacological actions: All the pharmacological effects of captopril are attributable to its single known action viz. inhibition of conversion of angiotensin I to angiotensin II. It thus prevents the two principal effects (pressor effect and stimulation of aldosterone synthesis and secretion by the adrenal cortex) of endogenous as well as intravenously injected angiotensin I. As a consequence of inhibition of angiotensin II synthesis, the plasma levels of renin and angiotensin I show a marked compensatory rise. ACE also metabolises bradykinin (see Chapter 21). Inhibition of ACE raises the levels of bradykinin, a potent vasodilator.

In healthy, sodium replete animals and humans, a single oral dose of captopril lowers the systemic blood pressure only slightly; the effect is more marked on repeated administration. By contrast, a single dose of captopril causes substantial lowering of blood pressure in salt depleted subjects.

In hypertensive subjects, captopril lowers systemic arterial resistance and the mean, systolic and diastolic blood pressures. Although the initial reduction in blood pressure correlates well

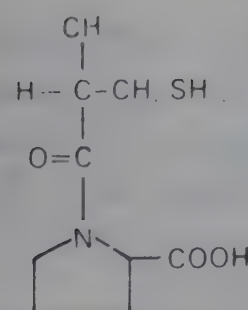


Fig. 26.7 : Captopril

with the pre-treatment renin-angiotensin status of the subject, the sustained lowering during chronic administration shows little or no such correlation. There occurs dilatation and increase in blood flow in the renal, cerebral and coronary beds. In addition, captopril increases the compliance of large arteries and thus contributes to the reduction in systolic blood pressure. Baroreceptor function and cardiovascular reflexes are not compromised and responses to posture and exercise are not impaired. The heart rate increases but little. The antihypertensive effects are seen in all varieties of hypertension (except that due to primary aldosteronism) but are most marked in patients with renovascular hypertension. They are potentiated by the concurrent use of a diuretic but addition of beta-adrenergic blocker is of less value.

Secretion of aldosterone is reduced but not seriously impaired. Adequate levels are maintained by other secretagogues, ACTH and potassium. As these secretagogues need a permissive level of angiotensin II for their action, it is obvious that the inhibition of ACE is not complete.

In patients with chronic, congestive heart failure, captopril produces several beneficial effects. As a result of decreased peripheral arterial resistance, the afterload is reduced; the cardiac output increases; the heart rate diminishes; systemic blood pressure falls initially but tends to return to pre-treatment levels. There occurs natriuresis as a result of hemodynamic changes and as a result of reduction in aldosterone secretion. The expanded volume of body fluid shrinks; there is reduction in venomotor tone; as a result of the two actions, the venous return to the heart

diminishes. There occur reductions of pulmonary arterial pressure, pulmonary capillary wedge pressure and of left atrial and left ventricular filling pressure (preload). Exercise tolerance increases. The drug is probably superior to hydralazine and prazosin.

Absorption, excretion and fate: Captopril is rapidly absorbed from the gut with a bioavailability of about 65%. Its absorption is reduced by food and so it should be given 1 hour before a meal. It is cleared rapidly from the body by renal excretion (95%); about 1/2 is excreted as captopril and the other half as metabolites.

Adverse reactions: Most of them are the result of the specific inhibition of ACE. A steep fall in blood pressure may occur after the first dose in subjects with severe hypertension who are on multidrug regimes including a diuretic, in patients with congestive heart failure treated vigorously with diuretics, and generally in all salt depleted patients. In such patients, captopril should be started in very small doses, preferably after stopping the diuretic. Serious hyperkalemia is uncommon. However, the concurrent use of a potassium sparing diuretic should be avoided. Renal insufficiency has been reported in patients with hypertension due to bilateral renal artery stenosis.

Captopril is generally well tolerated. The adverse effects are skin rashes, loss of the sense of taste, vitiligo, headache and G.I. disturbances. Neutropenia is a serious but rare effect. Proteinuria (>1 g/day) has been described. Sometimes it causes persistent dry cough and rarely angioneurotic edema.

Preparation and dosage: Captopril is available as 25, 50 or 100 mg tablets. The drug should be taken 1 hour before a meal. The initial starting dose in adults is 12.5 mg two times a day. It is increased once in 1-2 weeks to a maximum dose of 50 mg. two times a day; however a dose larger than 150 mg. per day is rarely required. In patients who are likely to be over-responsive to the effects of captopril (see above), and those taking diuretics the initial dose should be 6.25 mg or less. Because of reduced clearance, smaller

doses than usual are also indicated in patients with impaired renal function.

Therapeutic uses:

(1) **Hypertension:** Used judiciously, captopril is useful in hypertension of all grades including malignant hypertension. When used alone, captopril is roughly comparable to a thiazide diuretic or a beta adrenergic blocker. It can be combined with a diuretic. It can be used in asthmatics and diabetics. There is little tendency to weakness and sexual dysfunction. There is no rebound hypertension on stopping the drug abruptly. It is not recommended as a first line treatment, but should be used in patients with moderate to severe hypertension, who fail to respond to standard therapy or as an adjunct to diuretic therapy.

2. **Chronic congestive heart failure:** See Chapter 24.

Enalapril: This congener of captopril does not contain sulphydryl group. It has actions similar to those of captopril and the same precautions apply to its use as to the use of captopril. However, it is more potent than captopril; its action is slower but lasts longer; food does not interfere with its absorption. It is a prodrug and is converted to the active metabolite enalaprilic acid in the body; the latter is poorly absorbed from the gut. Hypotension and renal insufficiency are far commoner with enalapril than with captopril. Urticaria and angioneurotic edema have also been reported after enalapril. It, however, does not cause taste disturbances. In hypertension enalapril is a second choice after captopril. In patients with congestive heart failure, the starting dose should be 2.5 mg/day in subjects over 60 years of age and 5 mg/day in subjects younger than 60. It is available as 5, 10 and 20 mg tablets. It is given once daily. Usual maintenance dose is 10-20 mg. per day.

The addition of enalapril to conventional treatment in patients with severe congestive heart failure can reduce mortality and improve symptoms.

Captopril and enalapril are claimed to protect kidney function and decrease micro-albuminuria.

ria in patient of diabetes mellitus with insulin dependent diabetic nephropathy.

SPIRONOLACTONE: This is an aldosterone antagonist and is discussed in Chapter 35. As an alternative to thiazides, it may be particularly useful in patients with significant hyperuricemia, hypokalemia, or glucose intolerance. It is the drug of choice in primary hyperaldosteronism.

VIII. Oral diuretics and related compounds:

The diuretics of the benzothiadiazine group and a related phthalimidine compound chlorthalidone have proved extremely valuable in the treatment of mild to moderate hypertension. In addition, they enhance the effect of other hypotensive agents like reserpine, vasodilators, the adrenergic neurone blockers and methyldopa.

Pharmacological actions: The detailed pharmacological actions of these compounds are discussed in Chapter 35.

The antihypertensive effect of chlorothiazide and its congeners develops slowly. There is a reduction in the systolic and the diastolic blood pressure. The hypotensive action is mild, the maximum effect being obtained with 50 mg of hydrochlorothiazide or an equivalent amount of any of its congeners. Increase in the dose does not enhance the hypotensive effect and there appears little difference in their antihypertensive action in equivalent doses. Differences do exist, however, in their duration of action which is similar to that of their diuretic action (see Chapter 35). The very potent diuretics frusemide and ethacrinic acid are not recommended for the long term management of hypertension because of their short duration of action and the serious electrolyte disturbances they could produce. However, they can be valuable in patients with kidney disease who do not respond to thiazides.

The thiazides probably reduce the blood pressure by several mechanisms. The sodium depletion and consequent reduction in plasma volume and cardiac output produced by them are important in the initial days of treatment of essential hypertension. The same is probably true of the

sodium and water dependent form of hypertension in chronic renal failure. It is well known that severe dietary restriction of sodium can produce a similar fall in blood pressure in these two situations. After a few weeks of thiazide therapy, the plasma volume and the cardiac output return to the pre-treatment level in essential hypertension. From then on, reduction in interstitial fluid volume and consequent decrease in vascular wall stiffness and increase in vascular compliance are important factors in maintaining the antihypertensive effect of the thiazides. However, as anephric patients do not show a reduction of blood pressure on thiazides, ultimately saluresis appears to be critical to their effect. When GFR is reduced by 50% or more, thiazides lose most of their diuretic and antihypertensive effects. Concurrent administration of NSAID causes sodium retention and a loss of control of blood pressure by thiazides and other diuretics. Routine potassium supplementation of hypertensives on thiazides is not necessary. Those at high risk of developing complications of hypokalemia (patients with ischemic heart disease, arrhythmias, diabetes, severe hepatic disease as well as those on digitalis or glucocorticoids) should receive potassium supplements prophylactically. If hypokalemia does develop, potassium sparing diuretics are more effective than potassium supplements.

Adverse reactions: These include hypokalemia, hyperuricemia and hyperglycemia.. See Chapter 35. However, the claim that hypokalemia and increased serum cholesterol levels may be dangerous is not supported by recent evidence. These data indicate that (a) in the absence of digitalis and possibly overt heart disease, the hypokalemia is not associated with increased occurrence of ventricular arrhythmias; and (b) although serum cholesterol levels do rise modestly after thiazide diuretic dosing, the levels usually revert to the pre-treatment levels during long term therapy. *The oral thiazides remain as our most valuable antihypertensive drugs.*

INDAPAMIDE (Natrlix): This new com-

pound, an indole derivative of chloro-sulphonamide, is chemically related to chlorthalidone. Like the latter drug, it has a long duration of action with a plasma $t_{1/2}$ of about 18 hours. Given orally in the dose of 2.5 mg. once daily, it can reduce the blood pressure in mild and moderate hypertension. Larger doses cause diuresis and associated electrolyte disturbances. The drug appears to have similar therapeutic activity as chlorthalidone and can be combined with other antihypertensive drugs. It is available as 2.5 mg. tablets.

XIPAMID : This is 4-chloro-5-sulfamoyl-2'-6' salicyloxlidide. The drug has diuretic and hypotensive effects as well as adverse effects similar to thiazides. Like thiazides, it acts on the distal tubule. It also resembles furosemide in that it is an effective diuretic in patients with renal failure. It is generally administered in a single daily dose of 20-40 mg. It is available as 20 mg. tablets.

IX. Miscellaneous drugs:

PARGYLINE is an M.A.O. inhibitor (see Chapter 11) with a hypotensive effect. It is now rarely used in the treatment of hypertension because of its adverse reactions and drug interactions. For details see the previous edition of this book.

METYROSINE (Alphamethyltyrosine): This drug blocks the synthesis of catecholamines by inhibiting tyrosine hydroxylase. It has been found useful in the preoperative treatment of patients with pheochromocytoma, as well as in the long term management of those in whom surgery is not feasible. The adverse effects include sedation, G.I. symptoms, extrapyramidal effects, crystalluria, nasal congestion, gynecomastia, galactorrhoea and peripheral edema. It is available as 250 mg capsules. Therapy is commenced with 250 mg four times daily and the dose is gradually increased by 250-500 mg daily to a maximum of 3 g daily. *It is not indicated in essential hypertension.*

DRUG THERAPY OF HYPERTENSION

Effective treatment of hypertension is an important part of any programme to reduce the toll of 'cardiovascular disease' in the society. This is so because actuarial studies have shown that any elevation of blood pressure significantly increases morbidity and mortality which are directly related to the level of the blood pressure.

The drug treatment of hypertension is still 'empiric', as these drugs reduce the blood pressure without correcting the cause. In spite of various limitations of antihypertensive drugs and the difficulties presented by their long term use, it is now generally accepted that the reduction of blood pressure prevents or postpones renal, cardiac and cerebral complications and prolongs life. The control of hypertension in diabetics helps to delay the onset of retinal and renal damage. Complications arising from associated atherosclerosis are now the chief cause of death.

Thorough pre-treatment evaluation of a hypertensive patient is indispensable.

The initial assessment should include:

- (i) Multiple readings of blood pressure after sufficient rest, in both standing and supine positions.
- (ii) Urine examination, serum creatinine, serum electrolytes and serum calcium.
- (iii) X-ray chest and E.C.G.
- (iv) Fundoscopy for retinal changes.
- (v) Assessment of other cardiovascular risk factors (family history of ischemic heart disease, diabetes, hyperlipidemia etc.).

The state of cerebral vessels may be gauged by examination of fundi, as both cerebral and retinal vessels react similarly to nervous stimuli as well as pharmacodynamic agents.

Intravenous pyelography, tests for pheochromocytoma, renal angiography and plasma renin profiling are carried out (a) where specific indications are present and (2) in patients who prove resistant to initial drug therapy.

Selection of patients: Every patient who knows that his or her blood pressure is elevated requires treatment though it is not necessary with

hypotensive drugs. The initial aim of treatment is to achieve and maintain diastolic blood pressure below 90 mm Hg. In many patients, nonpharmacological treatment suffices. It comprises (1) reassurance, (2) weight reduction in obese patients, (3) restriction of salt intake to 75 mEq (4 - 5 g) per day, (4) increase in potassium intake, (5) reduction in alcohol consumption and (6) better adjustment at job and in family life. In some cases, treatment with antihypertensive drugs would be necessary. It should be noted that :

(a) It is now believed that systolic hypertension is as damaging as (if not more damaging than) diastolic hypertension.

(b) Treatment with hypotensive drugs should not be undertaken lightly since once started, in all probability, it will have to be continued for life.

(c) Success of the treatment depends considerably on the time and care devoted by the doctor and the co-operation given by the patient.

Clinically, hypertension can be divided into mild, moderate and severe grades (Table 26.1).

Patients with diastolic pressure of 130 mm Hg or more are at grave risk of developing one of the typically 'hypertensive complications' such as cerebral hemorrhage, hypertensive encephalopathy, acute left ventricular failure, renal failure or dissection of the aorta. All these patients and those with papilloedema (malignant hypertension) need urgent and aggressive treatment with the potent antihypertensive drugs available. The beneficial effects of antihypertensive drug treatment were convincingly demonstrated first in such patients.

Patients with diastolic pressure between 115

and 130 mm Hg are also at grave risk of developing the same 'hypertensive complications' especially if they have cardiomegaly, electrocardiographic abnormalities or abnormal fundus changes. Men are at greater risk than women. The older the patient and the longer the duration of hypertension, the closer is a 'hypertensive complication'. Although the risk of a fatal complication is less in young patients, they are more liable to suddenly develop malignant hypertension. Prompt treatment of these patients can ward-off a 'hypertensive complication' but unfortunately does not slow down the accelerated rate of atherosclerosis.

Patients with diastolic blood pressure between 105 to 115 mm Hg are also at risk if they have a bad family history (a near relation has had a 'hypertensive complication') or if they have cardiomegaly, fundus changes or electrocardiographic abnormalities. They too require energetic treatment of their hypertension.

If the diastolic pressure is less than 105 mm Hg, the need for treatment is determined by the patient's age. Studies by the Veteran's Administration have shown that young patients in this group definitely benefit from aggressive treatment of their hypertension. *Reduction of blood pressure is, however, likely to prove dangerous in elderly arteriosclerotic individuals with elevated systolic but normal diastolic blood pressure.* If the diastolic blood pressure is 90 - 104 mm Hg, nonpharmacological treatment should be given a trial for six months. If it does not lower the diastolic blood pressure to less than 90 mm Hg, treatment with antihypertensives is indicated, especially if additional cardiovascular risk fac-

Table 26.1: Grades of hypertension

Diastolic B.P. (mm.Hg.)	Optic fundi changes (Grade)	Cardiac and /or renal damage	Grade
90-105	I	Nil	Mild
105-115	I or II	Moderate	Moderate
115 and above	III or IV	Severe, rapidly progressing	Severe

tors are present. If diastolic blood pressure is below 90 mm Hg but other cardiovascular risk factors are present, non-pharmacological treatment should be initiated.

Maternal hypertension increases the risk of miscarriage and foetal mortality, so that during pregnancy a sustained diastolic hypertension of 100 mm Hg or over requires control. An adequate control in such cases much improves the prospect of the mother going to term with a healthy child.

In patients with hypertension and renal failure, there may be an initial deterioration of renal function after starting antihypertensive drug treatment. In the long run, however, effective control of arterial pressure halts the downhill progress of renal failure and prolongs life in these patients.

Antihypertensive drugs should be used extremely cautiously in patients who have had a recent myocardial infarct or a stroke, as a rapid lowering of blood pressure can worsen their condition.

The duration of drug treatment is lifelong in most patients. An occasional patient gives up his treatment and remains normotensive thereafter. How often this happens is not known but it is probably not common.

Principles and aims of drug therapy :

(1) In practice, one aims at keeping the blood pressure in the erect posture as near normal as possible. This generally means a diastolic pressure of 80-90 mm Hg. However, a higher level of blood pressure may have to be accepted in elderly patients, in patients with impaired renal function and in those with ischemic heart disease or cerebrovascular disease. This is done in order to avoid the unpleasant symptoms and the possible complications (including myocardial and cerebral infarction) of postural hypotension.

(2) With drugs such as beta-blockers, methyldopa and clonidine, which do not cause significant postural hypotension it is possible to maintain not only standing but also supine blood pressure normal or near normal in some patients. If this can be done safely and continuously, then

this is almost ideal antihypertensive therapy.

(3) Doses of antihypertensive drugs should be increased gradually and only infrequently as the maximum hypotensive effects of a drug or drug combination at a given dose level may not be manifested for some days or weeks.

(4) Having found a regime that controls blood pressure in the best possible manner, it is wrong to change the schedule unless there is a good reason to do so. However, in hot weather the patient may be asked to reduce the doses of antihypertensive drugs slightly in order to avoid postural hypotension. The fall in standing pressure may be exaggerated by exercise or sudden change of position and the patient should be warned of the possibility of fainting.

(5) During chronic therapy with drugs acting on the cardiovascular system, adjustments occur in homeostatic mechanisms including the reflex cardiovascular responses and in the end organ receptor concentration; for example, the number of beta adrenergic receptors increases during chronic propranolol therapy. The reaction of the patient to the abrupt cessation of drug therapy depends upon the duration of action of the drug and the readjustment time for the homeostatic mechanisms activated during drug therapy. If the former is much shorter than the latter (as is the case with propranolol and clonidine) rebound cardiovascular changes are likely to occur, with occasional lethal consequences. If, on the other hand, the former is prolonged compared to the latter (as is the case of guanethidine and reserpine) no such rebound occurs. Abrupt cessation of clonidine has been reported to produce a dangerous rebound rise in blood pressure with occasional cerebral hemorrhage. The patient should be warned about this.

(6) It is difficult to be familiar with more than a few preparations and hence, it is wise to continue using the one or two preparations which one knows best and change them only if they are ineffective or adverse effects are troublesome.

(7) Watch for possible drug interaction when the patient is on more than one drug.

(8) Impress upon the patient the hazards of

uncontrolled or intermittently controlled hypertension and the rewards of keeping the blood pressure under check continuously and lifelong.

(9) The patient on potent antihypertensive drugs must be given a card bearing the names and doses of the drugs he is receiving.

(10) Moderate salt restriction not only helps the antihypertensive effect of oral diuretics but also minimizes hypokalemia which is dependent on the sodium load presented to the distal renal tubules. *Hence, salt restriction should form a part of the routine management of hypertension.*

(11) The 'diabetogenic' effect of the thiazides is often overstressed in the literature. Similarly, unless specifically contraindicated, reserpine is a useful and relatively cheap antihypertensive drug.

Use of drug combinations: The appropriate combination of antihypertensive drugs can produce beneficial effects on:

- (a) Blood pressure.
- (b) Adverse reactions, and
- (c) Hemodynamic effects.

Except perhaps in cases with mild hypertension, most hypertensive patients would need combined drug therapy. It is rational to combine antihypertensive drugs with different pharmacodynamic activities or with different anatomical sites of action e.g. a diuretic can be combined with a betablocker, reserpine, a vasodilator, methyldopa, captopril or guanethidine. On the contrary combination of drugs like guanethidine and reserpine is not expected to give any synergistic effect due to similarity in actions. Methyldopa and clonidine have similar adverse effects such as drowsiness and dry mouth and there is no advantage in combining them. Similarly, the combination of clonidine and a beta blocker can cause excessive drowsiness.

The drugs which interfere with the adrenergic system tend to produce fluid retention. Addition of a thiazide effectively counteracts this fluid retention, enhances their antihypertensive effect and permits the use of smaller doses of the more potent drug.

Drug combinations not only help to get better

blood pressure control but also reduce the incidence of adverse effects due to any one drug because of individual reduction in dosages. Furthermore, certain drugs, when combined, can reduce adverse effects by pharmacological means e.g. tachycardia produced by hydralazine can be countered by reserpine, guanethidine or propranolol which produce bradycardia.

Such combinations, however, should be decided upon by the physician with full knowledge of clinical pharmacology of the drugs he is using. Widely advertised readymade combinations which contain fixed amounts of antihypertensive drugs should not be encouraged as therapy in such form interferes seriously with the adjustment of the dosage.

Management with drugs:

There appear to be two major factors in human hypertension : expansion of plasma volume (correctable by a diuretic) and peripheral vasoconstriction (correctable by antiadrenergic drugs).

Although LREH patients probably respond more readily to diuretics than do HREH patients and the latter respond more readily to drugs which interfere with the adrenergic nervous system, *the majority of hypertensive subjects will have blood pressure reduction no matter what drug is used.* Hence, the initial choice of the drug should depend upon such factors as safety, cost, likely patient compliance and associated medical problems which may either benefit from a given drug or increase the liability to adverse effects. Such *symptom drug profiling* (Table 26.2) is likely to prove more useful in practice than *renin profiling* in hypertensive patients.

In recent years, a stepped-care-approach has been recommended in the drug treatment of hypertension. Initially, treatment is started with small doses of a single drug. The dose of that drug is increased till the desired blood pressure level is achieved without undue adverse effects or until the maximum recommended dose is reached. At that point, additional antihypertensives are added in a stepwise manner. Table 26.3 outlines one

Table 26.2 : Symptom profiling of Antihypertensive drugs

Problem	Possibly beneficial	Possibly deleterious
Headache	Beta blockers, Clonidine	-
Anxiety	Reserpine, Clonidine, Methyldopa	-
Depression	-	Reserpine, Clonidine Methyldopa.
Postural dizziness	-	Vasodilators Guanethidine
Bronchospasm	-	Beta blockers especially propranolol
Palpitation	Beta blockers, Clonidine, Guanethidine	Vasodilators
Angina, old myocardial infarction	Beta blockers, Calcium antagonists	Vasodilators
Constipation	Reserpine, Guanethidine	Clonidine
Diarrhoea	Clonidine	Reserpine, Guanethidine
Renal insufficiency	Methyldopa, Hydralazine, Clonidine.	Guanethidine
Fluid retention	Diuretics	Vasodilators, Clonidine, Betablockers.

recommended approach to stepped care.

From the point of view of treatment hypertension is generally grouped into: (1) mild, (2) moderate and (3) severe grades as shown in Table 26.1.

Table 26.3: Stepped Care Approach to Drug Therapy of Hypertension

Step 1 : One drug. Either a thiazide diuretic or a beta blocker.

Step 2 : Two drugs. The second drug may be either a thiazide diuretic or a sympatholytic agent (beta blocker, reserpine, clonidine, prazosin or methyldopa). Captopril may be substituted if the above drug is ineffective or produces unacceptable adverse reading.

Step 3 : Three drugs. The third drug may be a vasodilator (hydralazine; minoxidil in resistant cases), captopril or a calcium channel blocking agent.

Step 4 : Four drugs. Add guanethidine or captopril.

Mild hypertension: The basic drug in the treatment of mild hypertension is hydrochlorothiazide or any of its congeners unless a specific contraindication for the use of these agents exists. Hydrochlorothiazide is administered initially in the dose of 25 mg. twice daily; any of its congeners can be employed in equivalent dosage. Increasing the dose beyond 100 mg. daily of hydrochlorothiazide usually does not produce any further therapeutic benefits in most patients. The hypotensive effect is usually established within a period of 2 to 3 weeks. Subsequently smaller doses can be administered to achieve a maintenance effect.

Sedatives, even though devoid of any direct hypotensive effect, play an important part particularly in the treatment of mild hypertension. Compound like diazepam are usually employed for this purpose.

If the blood pressure is not adequately controlled by diuretics, the therapy can be intensified with the addition of reserpine or a beta-blocker. Reserpine is used in the dose of 0.1 to 0.25 mg daily. Although further therapeutic effect may be obtained at higher doses, serious toxicity usually limits the dose that can be given safely. The entire daily dose is administered as a single dose. Propranolol is generally started in the dose of 20 mg. 2-3 times a day and is gradually increased upto a maximum of 100 mg. three times a day. Reserpine, however, is much cheaper than beta-

blockers at present.

If the patient is younger than 50 years of age and has evidence of tachycardia and hyperdynamic cardiac action, a betablocker may be initial drug of choice, especially if there is no evidence of peripheral vascular disease. The presence of ischemic heart disease is another indication for the use of betablockers.

Moderate hypertension: In moderate hypertension, hydrochlorothiazide or chlorthalidone in combination with either reserpine or a betablocker may not be able to control the blood pressure effectively. Change-over from reserpine to clonidine or from betablocker to alphas-methyldopa is called for; alternatively, prazosin may be added as a third drug, to establish satisfactory blood pressure control.

Clonidine is started in the dose of 0.1 mg 3 - 4 times a day and the dose is gradually increased to 2 mg per day. Major part of the dose is given at bedtime.

Alpha methyldopa may be used instead of clonidine along with a thiazide in the treatment of moderate hypertension. Dosage is 250 mg. two, three or four times a day to start with and the daily dose is increased by 250 mg. at intervals of 2 to 7 days to a maintenance level. Alpha methyldopa alone usually cannot control blood pressure adequately in such cases. Doses below 500 mg. are not effective and the hypotensive effect does not increase further with doses larger than 3 g. per day. Usually, doses of methyldopa larger than 1.5 g. daily should be avoided because above this level mental and physical apathy become intolerable in majority of patients.

For details of prazosin, see earlier.

Severe hypertension: Patients with severe hypertension usually have substantially damaged kidneys and heart. Therapy has to be undertaken with caution in such patients as a sudden reduction in blood pressure may produce azotemia or coronary insufficiency. If, however, the diastolic blood pressure is above 120 mm Hg and there is no evidence of organic damage, vigorous therapy is advocated.

Treatment of severe hypertension may require

administration of three drugs. The third drug may be a direct acting peripheral vasodilator (hydralazine, or in resistant cases minoxidil), a calcium channel blocker or captopril.

Hydralazine is usually started in small doses because of its disturbing adverse effects. The initial dose is 10 mg twice daily and is then gradually increased to 50 - 100 mg twice a day. The upper limit of 400 mg should not be exceeded for fear of appearance of rheumatoid arthritis-like syndrome. Hydralazine is particularly useful in the presence of kidney damage as it dilates the renal vessels. It is contraindicated in patients with arteriosclerotic hypertension, in those with congestive cardiac failure and in all who have angina or myocardial infarction. Peptic ulcer is also a contraindication. Hydralazine exhibits synergistic effect with hydrochlorothiazide and its congeners.

Calcium channel blockers, verapamil and nifedipine, are effective anti-hypertension agents. Because of its negative inotropic action, verapamil is contraindicated if congestive heart failure or AV block is present, and in patients on digitalis or a beta blocker. Nifedipine is safer in these circumstances. However, nifedipine elicits reflex sympathetic overactivity with tachycardia and increased cardiac contractility.

Captopril may be a good drug to add if the patient is also in congestive cardiac failure. Captopril (in the dose of 25 - 50 mg twice daily) may be the preferred drug in hypertensive patients with diabetic nephropathy for several reasons: (a) it does not alter glucose tolerance; (b) it does not mask the symptoms and signs of, nor interfere with recovery from, hypoglycemia; (c) ACE inhibitor would appear to protect the kidney by improving the GFR.

Guanethidine may be added in resistant cases. It is usually started in a dose of 10 mg. once a day and is increased weekly by 10 mg. The maximum dose recommended is 400 mg. per day. There are considerable inter-individual variations in the dose requirements: 10 mg. to over 100 mg. per day.

Hypertension in the elderly: Both isolated

systolic and diastolic high blood pressure are cardiovascular risk factors in the elderly and need attention. The beta adrenergic responses of vascular smooth muscle clearly declines with age; plasma renin levels also decline with age. The most consistent cardiovascular physiologic change in elderly patients is increased peripheral resistance.

Antihypertensive drugs must be used cautiously in old people. Not all hypertension in all old people needs drug treatment; this is especially so in patients over 70 years of age. Treatment should be considered for those elderly patients whose blood pressure exceeds 160/100 mm Hg. Rapid lowering of blood pressure and postural hypotension can be dangerous and must be avoided. Sometimes, unpleasant hypotension can occur on exertion and this too must be avoided. Hence, it is advisable not to use adrenergic neurone blockers such as guanethidine, bethanidine and debrisoquine. Reserpine may cause serious depression in the elderly. Clonidine and prazosin are also better avoided because of their possible adverse effects. On the other hand, the low dose thiazides or methyldopa would appear to be relatively safe drugs in these patients. Doses of diuretics larger than the equivalent of 25 mg. of hydrochlorothiazide per day should be probably avoided and even mild hypokalemia treated with potassium supplement or potassium sparing diuretic, provided kidney function is normal. A beta-adrenergic blocker may also be used unless contraindicated by bronchospasm or incipient cardiac failure. *Complex, multiple-drug regimes are best avoided as they may be confusing.* Hypertension which persists after cardiac failure is corrected needs treatment with an antihypertensive drug whereas a patient with an established stroke in old age does not benefit from such therapy. In fact, some patients of the latter group may show an intellectual deterioration on lowering of the blood pressure and their hypertension is best left alone. The aim of therapy in the elderly should be to lower the blood pressure as much below 180/100 mm Hg as the patient can tolerate com-

fortably. No attempt should be made to make the blood pressure 'normal'. Further, isolated systolic hypertension (defined as systolic blood pressure over 160 mm Hg and diastolic blood pressure less than 95 mm Hg) is often resistant to treatment; attempts to treat it aggressively lowers the diastolic blood pressure to such an extent as to embarrass blood flow to vital organs.

Hypertension during pregnancy: Hypertension during pregnancy predisposes to pre-eclampsia; if severe, it can also lead to intra-uterine fetal retardation and fetal death. Hence, it deserves to be treated. Hypertension in pregnant women may be diagnosed when the systolic blood pressure is 135 mm Hg or more or when the diastolic blood pressure is 85 mm Hg or more. The most effective antihypertensive measure in pregnancy is complete bed rest with only bathroom privileges allowed. Methyldopa is effective, and is safe for the mother and the baby; it is the preferred antihypertensive drug in pregnant women. The alternative to methyldopa is betablockers; however, their safety is less well documented than that of methyldopa. In acute episodes of hypertension during pregnancy, nifedipine can be used safely. The pregnant women have low plasma volume and reduced cardiac output despite generalised fluid retention. Hence, diuretics should not be used except to treat cardiac failure or eclampsia with severe oliguria. Reserpine is known to cause nasal blocking in the newborn baby and puerperal depression in the mother. Adrenergic neurone blockers (guanethidine, bethanidine and debrisoquine), clonidine and beta-blockers are better avoided in pregnant women unless hypertension fails to be controlled by methyldopa.

Supportive treatment of hypertension:

(a) **General treatment:** Adequate rest, relaxation and sleep are highly desirable. Ambitions may have to be curbed or sacrificed for reasons of health. Reassurance along with intelligent use of tranquilizers or sedatives like diazepam could benefit the patient. The patient should

be explained in detail what 'moderation in all things' actually means for him. Yoga, meditation and relaxation techniques may be helpful. Very strict restrictions are, however, many times unnecessary, as Page has aptly remarked, "I firmly believe that those who follow directions minutely do better than the careless. But there are important areas of living in which we physicians know no more than others. Often when we don't know what to do we proscribe instead of prescribe ---- we forbid this or that of the things people often most enjoy. I suppose this characteristic is a hangover from the days when anything that was pleasurable was sinful. Whether we forbid smoking, alcohol and such, may make a good deal of difference as to whether people will think life worth living. I should therefore remind you that smoke and alcohol were the oldest known preservatives and that Winston Churchill was 100 proof of this observation."

(b) **Weight reduction**, in obese patients, by dietetic control is highly beneficial. Although sodium restriction is known to help the reduction in blood pressure, with the present day diuretic drug treatment rigid restriction of salt intake is rarely necessary; in fact, it may be dangerous.

(c) **Posture**: In hypertensive acute left ventricular failure, advantage may be taken of the postural hypotensive effect by making the patient sit up in the bed.

TREATMENT OF HYPERTENSIVE CRISES

Extremely high blood pressure may be found in completely asymptomatic patients. Long term treatment with gradual reduction of blood pressure is sufficient in them to prevent severe organ damage. On the other hand, in many situations (see Table 26.3) blood pressure must be reduced in several hours or even within one hour to prevent death or severe damage to vital organ functions; they constitute hypertensive crises and are characterized by some or all of the following:

(a) sudden or sustained rise of blood diastolic pressure to 120 mm Hg or more; (b) papilledema

(not always present); (c) evidence of progressive decrease in renal function; and (d) evidence of neurological dysfunction. It is possible with modern drugs to lower the blood pressure in a matter of minutes but that can be hazardous and is known to cause fatal hypotension, stroke, blindness and myocardial infarction.

Table 26.3 : Hypertensive Crises

- | | |
|-----|--|
| (A) | Hypertensive emergencies (lower BP in 1 hour) |
| | Hypertensive encephalopathy |
| | Intracranial hemorrhage |
| | Acute myocardial infarction |
| | Acute pulmonary edema |
| | Acute aortic dissection |
| | Eclampsia |
| | Hypertensive crisis in pheochromocytoma |
| (B) | Hypertensive urgencies (lower BP in 4-8 hours) |
| | Unstable angina |
| | Diabetic retinopathy |
| | Preeclampsia |
| | Tyramine ingestion during MAOI therapy |
| | Amphetamine or cocaine intoxication |
| | Rapidly progressing renal failure; hypertension with papilledema and vitreous hemorrhages; severe epistaxis. |

The drugs used in hypertensive crises are *intravenous* sodium nitroprusside, diazoxide, phentolamine or trimethaphan; *intramuscular* reserpine; *sublingual* nifedipine; and *oral* clonidine. Diuretics should not be used except to combat salt retention caused by diazoxide or to treat intravascular volume overload such as acute left ventricular failure.

Close monitoring by frequent blood pressure measurements is absolutely necessary. It is preferable to treat the patient in a cardiac bed in the sitting posture with a back rest; the feet should be hanging down with arms resting on a bed table in front. By using this posture, the necessary dose of a posturally acting drug can be reduced by half

or a third.

Blood pressure can be reduced quickly by using:

(a) **Sodium nitroprusside:** This agent has almost instantaneous onset of action and is most consistently effective. It is given by continuous infusion in 5% dextrose solution or in normal saline. Since it can cause a precipitous fall in blood pressure, the infusion should be titrated very carefully and patient supervised in intensive care unit. This is its main disadvantage. However, it is the drug of choice in the presence of myocardial infarction or pulmonary edema.

(b) **Diazoxide (Hyperstat):** It is a very rapidly acting (within 1-2 minutes) and consistently effective agent. A single dose often controls blood pressure for as long as 18 hours, without reducing the renal blood flow. It is given intravenously in the dose of 1-2 mg/kg (not exceeding 150 mg), injected in 10 minutes, followed (if needed) by similar doses every 15 minutes till the blood pressure is controlled. Alternatively, a slow infusion at the rate of 15 mg per minute can reduce the blood pressure in 20-30 minutes. Diazoxide is considered to be the preferred drug in the management of hypertensive emergencies but it is contraindicated in patients with myocardial infarction, pulmonary edema and dissection of the aorta because it causes tachycardia and increase in the cardiac work. Sodium nitroprusside is preferred in these situations. Further, diazoxide may cause hyperglycemia. The acute hypotensive effect of diazoxide tends to be greater in uraemic patients. Hence, greater caution should be exercised while using diazoxide in these patients.

(c) The use of *phentolamine* in hypertensive emergencies in patients with pheochromocytoma has already been discussed. *Trimethaphan* is generally used to produce *controlled hypotension* during surgery; however, it may also be used as a substitute for sodium nitroprusside in hypertensive emergencies; its onset of action is within 1-2 minutes.

(d) **Reserpine:** Given intramuscularly in the dose of 1 to 5 mg., it reduces blood pressure within 1½ to 3 hours. It could be repeated if

necessary every 4-8 hours and oral medication may be started simultaneously. It may, however, induce stupor or coma in hypertensive encephalopathy and may obscure the subsequent onset of complications in patients with stroke or hypertensive encephalopathy. Further, parenteral reserpine is known to cause gastrointestinal bleeding in an occasional patient. The drug besides having delayed onset of action (2-4 hrs.) may cause cumulative effect leading to severe hypotension.

(e) **Nifedipine:** Sublingual nifedipine is effective in lowering the blood pressure rapidly and safely. It is given in the dose of 10 mg; it acts within 2-3 minutes and the action lasts for 2-3 hours. In less urgent cases, it can be given orally in the dose of 10 mg at 6 hour intervals. If a sublingual preparation is not available, the patient can chew a 10 mg tablet for immediate local absorption and should swallow a second 10 mg tablet. Nifedipine is the drug least liable to aggravate regional blood flow imbalances and to cause ischemia of the brain, heart, eyes or kidney. It is the preferred drug in situations where intensive care facilities are not available.

(f) **Labetalol:** Labetalol is used as an adjunct to the vasodilators in order to minimise tachycardia in patients with acute myocardial infarction, acute aortic dissection and hypertensive crisis in pheochromocytoma. It is given by intravenous drip in the dose 1-2 mg/minute.

(g) **Clonidine:** Clonidine is given initially in the dose of 0.2 mg. followed by 0.1 mg. every hour, till a total dose of 0.7 mg is given or diastolic blood pressure has come down by 20 mm Hg or more. After about 6 hours, a diuretic is added and clonidine is administered at 8 hourly intervals.

Hypertensive crises should be treated in a hospital, preferably in an intensive care unit where facilities for invasive blood pressure monitoring are available. In the absence of such facilities, intravenously used drugs (see above) should be avoided. Drugs which reduce the perfusion of vital organs minimally or not at all are to be preferred in the treatment of hypertensive

crises. The patient should be treated in a strictly supine position to avoid orthostatic complications. The immediate aim should be a moderate reduction rather than normalization of blood pressure and diastolic pressures should not be lowered below 100 mm Hg. If renal function is greatly impaired even a small reduction in GFR may be enough to worsen renal failure. Drastic lowering of blood pressure may cause cerebral ischemia leaving permanent neurological deficit and other serious effects like angina, myocardial infarction and blindness. Reserpine should preferably not be used to control hypertension in the presence of hypertensive encephalopathy, head injury and intracranial hypertension. Similarly diazoxide should be avoided in the presence of acute coronary insufficiency and acute left ventricular failure, with pulmonary edema. In such patients, nitroglycerine (sublingually or by intravenous infusion) or nifedipine is the preferred drug. Finally, in eclamptic women, reserpine increases the likelihood of seizures and trimethaphan can cause fetal ileus and stop labour; both drugs are contraindicated in eclampsia.

Although these drugs are administered parenterally with precaution and care, the physician must be prepared to manage the occasional patient who develops excessive hypotension. Hence, noradrenaline should be kept ready to treat drug induced hypotension. Similarly, while using the diuretic therapy, attention must be given for maintaining adequate hydration to avoid oligemia.

REQUIREMENTS OF AN IDEAL ANTI-HYPERTENSIVE DRUG

(a) It should produce predictable reduction in

both systolic and diastolic blood pressure in supine as well as in erect position.

(b) It should have a rapid action of sufficient duration.

(c) It should not reduce circulation to vital organs like brain, kidney and heart and should be free from toxic effects.

(d) It should not produce tolerance on long term administration.

(e) It should synergise with other anti-hypertensive agents and should be cheap.

Of all the available agents, surprisingly, the thiazide diuretics come nearest to satisfying these requirements.

DRUG INDUCED HYPERTENSION

Drug induced hypertension may occur in patients receiving oral contraceptives, glucocorticoids, carbeneloxone, sympathomimetic drugs, tricyclic antidepressants and M.A.O. inhibitors. It is imperative, therefore, to enquire whether the patient is taking one of these drugs before planning antihypertensive drug treatment.

Many proprietary 'cold cures' and 'cough mixtures' contain drugs such as ephedrine, phenylephrine or phenteramine. Therefore, it is best to warn the patients on antihypertensive therapy to avoid such preparations as they may cause a sudden rise of blood pressure, particularly in those receiving adrenergic neurone blockers.

Angina pectoris is not a disease but a symptom of myocardial ischemia produced in a variety of ways. It develops as a result of an imbalance between the oxygen supply and the oxygen demand of the myocardium. Its onset and clinical modalities, therefore, are related to the physiology of the coronary circulation, the factors governing myocardial metabolism, and the mechanism regulating the genesis and appreciation of pain.

The design of the coronary circulation has three bad features :

(1) The coronary arteries are functionally end arteries. In health, there is little communication between the larger branches of coronary arteries although collateral circulation does develop in patients who have had infarcts.

(2) Unlike the skeletal muscle, the cardiac muscle shows almost maximum oxygen extraction at rest, as shown by the comparative values of oxygen saturation of coronary sinus blood (30 per cent) and skeletal muscle venous blood (60-70 per cent). Hence, during exercise the tissue demand for increased oxygen supply is met, at least partly, by increased oxygen extraction in the case of skeletal muscle, but in the case of cardiac muscle it can only be met by increasing the coronary blood flow. Such increase can be severely limited by coronary artery disease. Moreover, unlike the skeletal muscle the cardiac muscle has extremely limited capacity for anaerobic metabolism and, therefore, cannot incur 'oxygen debt'.

(3) The two most important factors influencing the coronary blood flow are the inflow (aortic) pressure and the resistance of the coronary

vessel bed. The latter depends on:

- (a) the state dilatation of the coronary arterioles, determined largely by local metabolites, and
- (b) the pressure exerted upon the coronary vessels from the exterior by the contracting myocardium of the left ventricle during systole. Thus, in contrast to other areas where the arterial blood flow is continuous, coronary arterial blood flow to the left ventricle is intermittent and mainly diastolic; whereas in the absence of pulmonary hypertension it is both systolic and diastolic in case of the right ventricle.

In spite of these bad design features, the coronary circulation has a very large reserve and the coronary flow can increase upto 500 per cent of the resting value in exercising healthy dogs.

Oxygen consumption of the myocardium rises with increasing heart size, heart rate, systemic blood pressure and myocardial contractility i.e. velocity at which the muscle shortens. The last three are increased by heightened sympathetic activity. Tachycardia increases the total systolic fraction of the cardiac cycle and the contractility of the myocardium. Thus, the myocardial oxygen consumption increases significantly during exercise and other states (emotional excitement, exposure to cold) with increased sympathetic activity. If, for any reason, the increase in coronary blood flow is unable to match this increased oxygen demand, angina develops. In each patient, there exists at a given time a threshold (angina index = heart rate x B.P.) at which angina occurs. The angina index is an index of the

myocardial oxygen consumption.

It has recently become apparent that spasm of the coronary arteries is important in the production of angina. It causes the variant angina of Prinzmetal (see below) and is responsible for angina of effort in some instances.

Angina of effort is precipitated by physical activity such as running, walking uphill or fast, lifting heavy objects, strenuous unaccustomed exercise and sexual intercourse. It is also brought on emotional excitement. The main pathophysiological factor would appear to be increased myocardial oxygen demand, induced by tachycardia and rise of blood pressure. *Variant angina of Prinzmetal* (Angina at rest) is characterised by chest pain at rest rather than during exertion or stress; the electrocardiogram shows ST elevation rather than depression. Vasospasm of the coronary arteries (alone or superimposed on atherosclerotic coronary artery disease) is believed to be responsible for this entity. The term *unstable angina* is used when the anginal pain becomes more frequent or more severe, lasts longer or starts occurring at rest as well.

METHODS OF MEASURING CORONARY BLOOD FLOW

Coronary blood flow studies have been carried out mostly either in animals or on isolated hearts. The data obtained from such studies, however, are many times inapplicable to human patients. Results obtained from studies on human hearts are, therefore, more important. Even in such studies, it has been observed that the responses of atherosclerosed and normal coronary vessels to a given drug differ. Important methods are:

(a) *In vitro*

(i) Perfusion of isolated dog heart in ventricular fibrillation. The object of these experiments is to study the effect of drugs on the coronary circulation without the influence of ventricular compression on the coronary bed.

(ii) Perfusion of the isolated heart: Revived human heart or the heart removed from a freshly killed rabbit is perfused through the aorta

(*Langendorff preparation*). The time required for the perfusion of a definite volume of solution is taken as a measure of coronary flow.

(iii) Response of isolated rings of coronary arteries to drugs.

All these '*in vitro*' methods measure the drug responses under highly unphysiological conditions.

(b) *In vivo*

(i) Coronary flow in anaesthetized dogs has been studied by various electrical and mechanical techniques such as rotameter or thermostromuhr. The latter instrument includes a thermocouple which is activated by the coronary flow and records temperature changes.

(ii) There is still no ideal method for measuring coronary blood flow in man. The earlier nitrous oxide method involves monitoring of coronary arterial and coronary sinus N_2O concentrations following breathing of N_2O and then calculating the coronary flow by applying Fick principle. Other methods presently used involve measurement of outflow with coronary sinus catheterization e.g. continuous thermodilution method and green dye dilution method. The green dye dilution involves infusion of green dye solution into the coronary sinus, while the thermodilution technic uses a catheter with two platinum electrodes and an internal indicator-thermistor, mounted inside the lumen.

Other important technics available at present use a gamma camera and radioactive tracer wash-out with either ^{133}Xe or ^{125}I -iodoantipyrine. The technic using electromagnetic flowmeter has been employed to study myocardial metabolism and coronary flow during open heart surgery to determine vein graft patency.

(iii) Coronary angiography is now an established method of visualising the coronary tree and has shown important differences between the response of normal and atherosclerotic arteries to drugs. Further, it has been shown that angina can occur in the presence of normal coronary arteriograms.

(iv) Stress test: This test is frequently employed for clinical evaluation of anti-anginal

drugs. Patients suffering from angina pectoris are subjected to exercise, and the amount of exercise which they can tolerate without the development of pain with concomitant E.C.G. changes is noted. The same procedure is then repeated after the drug administration. An increase in the exercise tolerance, as shown by a delay in the development of precordial pain and E.C.G. changes, is a measure of anti-anginal activity of the drug. Another approach is to administer 10 per cent oxygen by mask and calculate the time required for the pain to develop before and after giving a vasodilator. In both these tests, a placebo can be substituted for the drug under study.

DRUGS USED IN ANGINA PECTORIS

It should be noted that besides the coronary dilators, drugs which reduce cardiac work are apt to be effective in angina.

The agents currently available for the treatment of angina pectoris are:

- (1) Organic nitrates
- (2) Beta-adrenergic blocking agents
- (3) Calcium channel blockers and
- (4) Miscellaneous drugs.

ORGANIC NITRATES: Organic nitrates which are polyol esters of nitric acid are potent vasodilators and have been used successfully in the therapy of angina for over hundred years. Usefulness of nitroglycerine was discovered when William Murrell, a busy physician, observed in 1879 that 'from a consideration of the physiological action of the drug it would probably be of value in the treatment of angina'.

Pharmacological actions: All the effects of nitrates, except those produced by toxic doses, are mediated through the direct relaxant action on smooth muscles which is their primary pharmacological action. The relaxant effect cannot be blocked by any known pharmacological inhibitors. At the same time, nitrates do not alter the response of the smooth muscle cells to various parasympathomimetic and sympathomimetic agents.

Nitrates are now believed to act by mimicking the vasodilator action of endothelium derived relaxing factor (EDRF) identified as nitric oxide. Vasodilating organic nitrates are reduced to organic nitrites, which is then converted to nitric oxide. Nitric oxide activates the enzyme guanylate cyclase in smooth muscle, leading to accumulation of cyclic GMP which is responsible for vascular relaxation.

(a) Cardiovascular system:

(i) *Hemodynamic actions:* Nitrates cause a relaxation of the systemic venous as well as arteriolar bed. Venodilatation causes peripheral pooling of blood and a reduction in venous return and in cardiac output.

On the arterial side, relaxation is maximum in the large arteries (resulting in bounding pulse), followed by the arterioles (resulting in lowered impedance). The blood pressure falls, the systolic more than the diastolic, and reflex tachycardia occurs due to compensatory sympathetic overactivity. Syncope may occur if the patient is standing.

These actions on the systemic venous (capacitance) and arteriolar (impedance) vascular beds reduce respectively the preload (end-diastolic left ventricular pressure) and the afterload (resistance to left ventricular ejection) on the heart. The left ventricular work load and energy expenditure thus decrease as a result of nitrate therapy. The improvement in the left ventricular function as a result of this generally outlasts the measured pharmacological actions of individual doses of nitrates; this is of great importance in the therapy of angina pectoris.

Sublingual nitroglycerine (NTG) is predominantly a venodilator agent causing reduction of ventricular preload resulting in decreased load on the heart. Unlike sublingual nitrates, inhalation of amyl nitrite, which acts very rapidly, has preferential systemic arteriolar dilator action which thereby primarily lowers the impedance or afterload to ventricular ejection. Rapid arteriolar dilatation causes distinct fall in blood pressure and marked rise in compensatory sympathetic overactivity. Consequent tachycardia will increase

the need of oxygen by the myocardium which is a therapeutic disadvantage with amyl nitrite as compared to NTG in the treatment of angina.

(ii) *Coronary circulation*: A decrease in the coronary resistance and an increase in the total coronary flow have been demonstrated in normal laboratory animals and man. But, these effects are too transient to explain the therapeutic benefits of nitrates in angina. Moreover, in patients in angina the total coronary blood flow actually falls concomitantly with the reduction in blood pressure. Various studies have, however, demonstrated that nitrates bring about (a) dilatation of the large coronary arteries, (b) dilatation of collateral vessel, and (c) a redistribution of the coronary blood flow with improved perfusion of ischemic subendocardial areas in the myocardium. Moreover, chronic administration of nitrates promotes the development of interarterial anastomoses within the myocardium and increases the survival rate after experimental narrowing of a coronary artery in pigs.

(iii) *Effects in angina pectoris*: The relative contribution of the hemodynamic actions and the actions on the coronary circulation in the effective therapy of angina is still debated but the present evidence would point to the former as the more important mechanism of the anti-anginal action of the nitrates.

Nitrates help most patients with angina by increasing their exercise tolerance but without increasing their 'angina index'. They probably achieve this by reducing the oxygen consumption of the heart at submaximal exercise levels and thus extending the duration of such exercise. They, however, do not increase the maximum aerobic capacity of the heart. In such patients, they prevent the appearance of electrocardiographic changes of cardiac ischemia during exercise.

(iv) *Other vascular beds*: Nitrates cause dilatation of other vascular beds as well, viz. (a) the skin, giving rise to flushing, (b) the meningeal vessels, resulting in throbbing headache, (c) pulmonary vessels, with fall in pulmonary arterial pressure, and (d) kidneys, with a reduction in renal flow concomitantly with reduction in blood

pressure.

(b) *Other smooth muscles*: Nitrates cause relaxation of the smooth muscles of the gall bladder, the biliary ducts, the sphincter of Oddi, the bronchi and the gastrointestinal tract and reduce the spontaneous motility of the gut.

The ureteral and sometimes the uterine smooth muscle are also relaxed.

Preparations and dosage: The organic nitrates used in the therapy of angina pectoris are shown in Table 27.1. The most commonly used drug is glyceryl trinitrate or nitroglycerine.

For intravenous use, NTG is diluted in 5% dextrose or 0.9% saline. It is useful in the treatment of refractory chest pain of myocardial ischemia or infarction and is particularly useful in patients with refractory variant angina. It is administered in the dose of 5 µg/minute, increasing the rate every 3-5 minutes upto 80-100 µg/minute. This treatment needs close cardiovascular monitoring and should be used only where such facilities are available.

Absorption, fate and excretion: Amyl nitrite is rapidly absorbed from lungs and also from other mucous membranes after inhalation. It is partly metabolized in the body and partly excreted by the lung. Amyl nitrite is decomposed by the gastric juice and hence, cannot be administered by mouth.

Organic nitrates are readily absorbed from the sublingual mucosa and their effects are more rapid and more predictable after this route than after oral administration. This is so because after sublingual administration, they bypass the liver where they are rapidly metabolised by denitration, a process of reduction by the glutathione organic nitrite reductase system of enzymes. The denitrated products have very little vasodilator activity. With relatively small sublingual doses, the various organic nitrates have similar duration of action, 10-45 minutes. Small oral doses (0.6 mg of nitroglycerine or 5 mg of isosorbide dinitrate) are of doubtful value as antianginal agents. Large oral doses (6.5 mg of nitroglycerine, 30 mg of isosorbide dinitrate or 40-80 mg of pentaerythrityl tetranitrate, every 4-6 hours) which

Table 27.1 : Nitrate and Nitrite Preparations Available for Clinical Use

Drug Preparations	Dose	Action	Schedule	Remarks
Amyl nitrite Pearls 0.2 and 0.3 ml.	0.2-0.3 ml Inhl.	O: 10 sec. D: 5-10 min.	SOS	Yellow, volatile, inflammable liquid, with fruity odour, costly. The pearl, when broken, makes a loud noise. Immediate relief.
Glyceryl trinitrate (Nitroglycerine, Angised) Tab 0.3, 0.4 and 0.6 mg.	0.2-0.6 mg. Sl.*	O: 1-2 min. D: 15-40 min.	SOS	Explosive yellow fluid in tablet, sustained release capsule and ointment form. Volatile. Unstable in plastic containers. Store tablets in tightly closed amber, glass bottles, without cotton plugs, preferably in a fridge. Sublingual tablets give immediate relief. Capsules, oral tablets and ointment for prophylaxis.
Sustained release caps.	1.3 - 9.0 mg. P.O.	O: 60 min. D: 8 - 12 hrs.	8-12 hrly.	
2% skin ointment (15 mg. per inch) (Nitrobid)	½ - 2 inch	O: 15 min. D: 4-6 hrs.	4-6 hrly	
Transdermal	(variable)	O: 30 min D: 24 hrs.	daily	
Isosorbide dinitrate (Sorbitrate, Isordil) Tab. sublingual	2.5-5 mg. Sl.	O: 2-5 min. D: 1-2 hrs.	3-4 hrly.	Useful in immediate relief and in prophylaxis.
Tab - Oral	10-40 mg. P.O.	O: 15-30 min. D: 4 hrs.	6 hrly.	
Tab - sustained release	40-80 mg P.O.	O: 60 min. D: 6-12 hrs	8-12 hrly.	
Pentaerythritol tetranitrate (Peritrate) Tab. 10, 20 mg. 40 mg.	20-60 mg. P.O.	O: 15-30 min. D: 4-6 hrs.		Used in prophylaxis
Erythrityl tetranitrate (Cardilate) Tab. 5, 10 mg.	15-60 mg. P.O.	O: 15-30 min. D: 3-4 hrs.		Used in prophylaxis

* When the tablet, placed under the tongue, fails to produce local burning, flushing of the face and pounding in the head, it should be considered inert.
Tab. = tablets. Cap. = capsules; Inhl. = by inhalation; Sl. = sublingually; P.O. = orally; O = onset; D = duration.

exceed the metabolising capacity of the liver, however, produce beneficial hemodynamic effects and are useful in prophylaxis of anginal attacks. Nitroglycerine skin ointment has similar prolonged effect and is useful in prophylaxis.

Adverse reactions: (i) Headache is a common adverse effect of nitrates. However, it decreases gradually on repeated administration and can be controlled by aspirin.

(ii) Transient episodes of giddiness, weakness and other signs of cerebral ischemia associated with postural hypotension may develop after nitrate therapy. These are seen especially when the patient stands immobile. Anoxia may stimulate the central vagal nuclei and cold sweats, nausea, vomiting, involuntary passage of urine and faeces may accompany postural hypotension. Head-low position to augment the venous return and administration of oxygen quickly correct the nitrite syncope. *Marked hypotension may occur when nitrates are used along with potent antihypertensive drugs especially vasodilators or with propranolol*; it has also been reported following the ingestion of alcoholic beverages by a patient on nitrate therapy.

(iii) Tolerance to various pharmacological actions of nitrates and to headache develops after repeated administration. Cross tolerance is common. Withholding nitrates for 1-2 weeks usually re-establishes the original susceptibility.

(iv) Intolerance: Drug rash is occasionally seen with any of the organic nitrates but is observed most commonly with pentaerythritol tetranitrate. Circulatory collapse accompanied by pallor, restlessness and heart block may occur rarely.

Therapeutic uses of nitrates:

(i) The main therapeutic application of nitrates is in the treatment of angina pectoris.

(ii) Nitroglycerine has been reported to give dramatic relief in paroxysmal nocturnal dyspnoea of left ventricular failure.

(iii) Organic nitrates are sometimes used in the long term management of chronic heart failure due to ischemic heart disease (See Chapter 24).

(iv) Amyl nitrite inhalation and intravenous

administration of sodium nitrite are resorted to in the treatment of cyanide poisoning. Nitrites convert haemoglobin to methemoglobin and methemoglobin competes with cytochrome oxidase for the cyanide ion. Combination of methemoglobin with cyanide results in the formation of cyanmethemoglobin, a relatively non-toxic product.

BETA ADRENERGIC BLOCKING AGENTS: These drugs now occupy a position second only to that of nitrates in the therapy of angina. Their detailed pharmacology is discussed in Chapter 14. Only their actions relevant to antianginal therapy are discussed here.

Pharmacological actions: Exercise and emotional excitement induce angina in susceptible subjects by the increase in heart rate, blood pressure, myocardial contractility and oxidative metabolism, they cause through increased sympathetic activity. Beta-receptor blocking agents prevent angina by blocking all these effects. Moreover, they help to control hypertension in hypertensive patients in the resting state as well. Like the nitrates, beta-blockers increase the exercise tolerance without increasing the angina index and prevent both subjective and E.C.G. manifestations of cardiac ischemia. They also prevent arrhythmias precipitated by exercise and emotion and by other conditions associated with excessive sympathetic discharge. They reduce the frequency of anginal attacks and decrease the NTG requirement in most patients. In most patients, the net effect is a beneficial reduction in cardiac work load and myocardial oxygen consumption.

Long term follow-up studies have demonstrated definite prophylactic value of beta blockade in angina pectoris. Beta-blockers are now considered as the basal preventive medication for most patients with angina. They possibly decrease the incidence of myocardial infarction in these patients. They are combined with nitrates for chronic prophylaxis of angina. If there is evidence of cardiac decompensation, the patient should be digitalized before starting a beta-

blocker.

Long term use of betablockers after myocardial infarction has been shown to reduce the rate of re-infarction and sudden death in these patients. Betablockers have also been used intravenously within the first 12 - 24 hours of onset of myocardial infarction, with beneficial results. In experimental animals, this use of betablockers has been shown to reduce the size of the infarct.

Absorption, fate and excretion: See Chapter 14.

Adverse reactions: The important adverse reactions of relevance to antianginal therapy are: (a) precipitation or aggravation of congestive cardiac failure. This is treated with digitalis. Patients receiving both digoxin and a beta-blocker should be watched for the development of heart block; (b) development of severe syncope on using nitroglycerine or amyl nitrite in patients on a beta-blocker; (c) aggravation of angina and even development of myocardial infarction if the beta-blocker is suddenly omitted. Other adverse reactions to beta-blockers are discussed in Chapter 14.

Calcium channel blockers: Calcium is necessary for the excitation-contraction coupling in both the skeletal and smooth muscle. However, in contrast to the contractile activity of the skeletal muscle, the contractility of the cardiac and vascular muscle is highly dependent on the extracellular calcium concentration.

The major cardiovascular mechanism of action of the calcium channel blockers appears to involve their interference with the calcium entry into the myocardial and vascular smooth muscle, thus decreasing the availability of the intracellular calcium. Calcium transport in these sites involves three possible sites: (1) *Voltage dependent channel* which is controlled by a gate that opens and closes in response to a voltage gradient. Calcium channel blockers close this gate and thus inhibit the entry of extracellular calcium ions. This is the major action of these drugs. (2) *Receptor operated channel*, normally activated by an alpha adrenergic agonist, such as noradrenaline or angiotensin interacting with the alpha

receptors. Some of the effect of calcium channel blockers could be due to blocking of the effects of norepinephrine on the alpha receptors. (3) *Sodium channel exchange* which is important for the action of cardiac glycosides but not very relevant to the action of the calcium channel blockers. Experimental evidence suggests that different calcium channel blockers probably combine with different receptors and that they have some differences in their molecular site of action. Antianginal property of these drugs is probably due to (1) improvement in the coronary blood flow and (2) decrease in the oxygen demand of the heart due to reduction in systemic vascular resistance and blood pressure (after-load). The latter action appears to be the more important one.

The main actions of these drugs are as follows:

(1) *Negative inotropic effect:* These drugs depress the contractility of the myocardium, and decrease the cardiac work and myocardial oxygen consumption. This effect proves beneficial in the treatment of angina of effort. Verapamil is a more potent negative inotropic agent than nifedipine and hence cannot be combined with beta-blockers in the treatment of angina of effort; however, nifedipine can be used together with beta blockers in this condition.

(2) *Antiarrhythmic effect:* Verapamil is particularly potent in this respect. Calcium channel blockers decrease the rate of discharge of the S.A. node, suppress ectopic pacemaker activity, increase the refractoriness of the A.V. node and slow the conduction of a propagated impulse in the myocardium (see Chapter 25). The slowing of the conduction prevents re-entrant excitation. This effect plus the improvement of cardiac ischemia (by decreasing myocardial oxygen consumption) account for the potent (though selective) antiarrhythmic action of verapamil. As discussed in Chapter 25, intravenous verapamil is the drug of choice in terminating paroxysmal, supraventricular tachycardia. Because verapamil (but not nifedipine) can aggravate A.V. block it must be used with caution in patients with de-

pressed A.V. conduction including that due to digitalis glycosides. Nifedipine is safer in such patients, if a calcium antagonist is indicated.

(3) *Cardioprotective effect*: These drugs have been shown to limit the size of experimentally induced myocardial necrosis of ischemic origin in animals. The importance of this effect in clinical use of calcium antagonists is not known.

(4) *Effect on coronary arteries*: These drugs are more potent than nitroglycerine as coronary artery dilators. Further, nitroglycerine dilates the large epicardial branches of coronary arteries but not the smaller intramyocardial coronary arterioles; calcium antagonists dilate both, even in the presence of coronary artery spasm. Further, they can prevent the spasm even in diseased, atherosclerotic coronary arteries. Nifedipine is a more potent coronary vasodilator than verapamil. This effect accounts for the efficacy of these drugs in vasospastic angina at rest (variant angina of Prinzmetal); and, it contributes to their effectiveness in angina of effort.

(5) *Effect on peripheral blood vessels*: Calcium channel blockers relax the vascular smooth muscle in systemic as well as pulmonary arterial circulations. They thus decrease the vascular resistance and the blood pressure in both these territories. They have been used with beneficial effect in the treatment of systemic and idiopathic pulmonary hypertension. Further, reduction in the afterload contributes to their efficacy in angina of effort. Nifedipine is a more potent vasodilator than verapamil. The reduction in blood pressure is accompanied by reflex tachycardia in the case of nifedipine but not in the case of verapamil which suppresses the S.A. node. They have little effect on the venous (capacitance) bed and do not alter the cardiac preload.

Thus, there are important differences in the degree to which nifedipine and verapamil exert various effects. Table 27.2 lists the important differences. These differences can be exploited to the patient's advantage in the therapeutic use of calcium antagonists. As a group, these drugs can be used in patients with chronic obstructive lung

disease in whom beta blockers are contraindicated.

VERAPAMIL (Cordilox, Isoptin): This drug is a synthetic papaverine derivative. In contrast to nifedipine, it is a more potent negative inotropic agent; it causes suppression of S.A. node; it possesses potent antiarrhythmic effect; it can cause A.V. block. On the other hand, it is less potent as a coronary and peripheral vasodilator than nifedipine. It is unsafe to use it together with beta-blockers and digitalis; nifedipine is safer in these situations. It is contraindicated in patients with severe congestive heart failure unless the

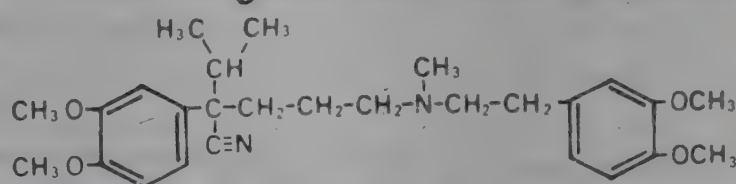


Fig. 27.1 : Verapamil

latter is due to supraventricular tachycardia. It is also contraindicated in the presence of cardiogenic shock. Unlike with nifedipine, there is no reflex sympathetic overactivity and tachycardia.

Given orally, it is absorbed completely, but is substantially metabolised by first pass hepatic metabolism. Hence, much larger doses are needed by oral route than by I.V. route for therapeutic effects. In the circulation, it is highly protein bound. Adverse effects include constipation, vertigo, bradycardia, heart block, congestive cardiac failure and hypotension. Rarely, it may cause cardiac asystole.

It is available as 40 mg tablets. It is used in the treatment of angina in the dose of 40-80 mg 3-4 times a day.

Its use in paroxysmal supraventricular tachycardia is described in Chapter 25 and in hypertension in Chapter 26.

NIFEDIPINE (Adalat, Caldigard, Calbloc): The pharmacological properties of this dihydropyridine derivative have already been described. It is also a potent inhibitor of platelet aggregation. It is available as capsules containing 10 mg. of a powder and can be used either orally

Table 27.2 : Properties of Calcium Channel Blockers.

	Verapamil	Diltiazem	Nifedipine
Vasodilatation	++	+	+++
Hemodynamic performance	Slightly ve.	No change	Improved
Blocks reflex sympathetic effects	+	++	0
Affects A-V conduction	+++	++	0
Dosage (mg/day)	240-480	120-360	30-120
Dosage schedule	8 hourly	8 hourly	6-8 hourly
Side - effects	A-V. block; constipation, nausea; can pptate LVF.	A-V block, hypotension, <i>Rarely</i> pptate LVF	Palpitation; hypotension; nausea; edema.

+ = Mild effect; ++ = Moderate effect; +++ = Potent.

or (for a rapid effect) sublingually. Orally, it is given in the dose of 5 mg. 3 times daily, with food, increasing the dose gradually upto 20 mg. 3 times a day. The contents of a capsule are placed under the tongue for sublingual administration. Its adverse effects include headache, tachycardia, dizziness, fatigue, orthostatic hypotension, leg cramps, skin rashes and gingival hyperplasia. Occasionally, congestive cardiac failure may be precipitated. Coronary artery spasm has been reported following rapid withdrawal during chronic therapy. Its main use is in the treatment of variant angina refractory to nitrate therapy. It has also been used in the treatment of hypertension and hypertensive emergencies (see Chapter 26).

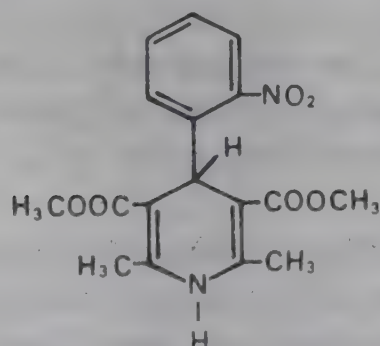


Fig. 27.2 : Nifedipine

Diltiazem and *lidoflazine* (Clinium, 60 mg tablets) are intermediate between verapamil and

nifedipine in their pharmacological properties. These four drugs are grouped as *potent and specific* calcium channel blockers. By contrast, perhexiline and prenylamine are less potent and less specific as calcium channel blockers. They are no more recommended. (See earlier editions for details)

Miscellaneous drugs:

PAPAVERINE: Papaverine, the alkaloid from opium, has been shown to be a coronary dilator in animal experiments but is of doubtful value in the treatment of human angina pectoris.

OXYFEDRINE (Ildamen): This compound has beta-adrenergic stimulant properties. Like other beta-adrenergic agonists it stimulates the heart, decreases peripheral vascular resistance and relaxes the smooth muscles. It can produce beneficial effects upon partial heart block and digitalis-induced bradycardia in man.

In experimental dogs the drug increases the infarct blood flow, peripheral coronary flow, heart rate and cardiac output and protects the animals against drug-induced arrhythmias. The drug is claimed to be useful in the long term management of angina pectoris including reha-

bilitation of patients with ischaemic heart disease. Further information, however, is needed to substantiate such claims and about its long term toxicity, particularly in view of its beta-receptor stimulant properties. It is available as 8 mg. tablets and 4 mg. in ampoules for injection.

DIPYRIDAMOLE (Persantin): This drug is a coronary dilator; but unlike nitrates which dilate conductance vessels it dilates coronary resistance vessels. It also has platelet inhibiting action. Though this increases coronary blood flow in experimental animals, it is disappointing in the treatment of angina pectoris. It, however, blocks platelet aggregation and is used as an antithrombotic drug (see Chapter 29).

TREATMENT OF ANGINA PECTORIS

The principles of treatment are:

- (a) Relief and prevention of individual attacks.
- (b) Chronic prophylaxis, which includes
 - (1) Use of nitrates, beta-blockers, calcium channel blockers and digitalis if needed.
 - (2) Advice about the way of life (physical exertion, emotional excitement, alcohol, smoking, over-eating).
 - (3) Treatment of associated diseases which act as aggravating factors.
 - (4) Supervised, graded, physical exercise training.
 - (5) Avoidance of preparations (cold remedies, antiasthmatic preparations and anorectic agents) containing sympathomimetic amines, atropine, aminophylline and anti-depressants, and
 - (6) Use of anti-atherogenic agents (see Chapter 36). Their value is not established.

Relief and prevention of individual attacks: Glyceryl trinitrate is the drug of choice in

all types of angina. A patient suffering from angina is advised to carry the tablets, and to put one sublingually as soon as premonitory symptoms develop. He should be advised to use nitroglycerine while sitting to avoid possible syncope. If symptoms are not relieved immediately, additional tablets may be used at 5 minute intervals, but not more than three tablets should be used in a 15 minute interval. He should discard the remaining tablets soon after the relief of pain, as excessive absorption of the drug would lead to hypotension. He may use as many tablets per day as he needs.

Nitroglycerine or isosorbide dinitrate, used sublingually 10-15 minutes before a period of increased activity such as walking, climbing or sexual intercourse, can frequently prevent the attack. This is the preferred method of using these drugs. The acute prophylactic effect of sublingual nitroglycerine and isosorbide dinitrate persists for about 30 minutes and 2 hours respectively. Longer prophylactic effect (upto 4 hours) is obtained with nitroglycerine cutaneous ointment as nitroglycerine is slowly absorbed and bypasses the liver.

Generally, isosorbide dinitrate causes less headache than nitroglycerine.

Chronic prophylaxis: This comprises:

(1) *Nitrates:* Large oral doses of organic nitrates decrease the frequency of anginal attacks and increase the exercise tolerance. They are useful in chronic prophylaxis of angina. They, however, increase the risk of hypotension, tachycardia and tolerance. Small oral doses are of doubtful value for this purpose.

(2) *Beta-blockers:* All beta-blockers seem to be equally effective as anti-anginal drugs and are the drugs of choice for chronic prophylaxis of angina of effort and can be combined, if necessary, with nitrates for this purpose. Generally, propranolol is started in the dose of 10 mg. 3-4 times a day. The daily dose is gradually increased (once in 3-4 days) by 20-30 mg. The dose is increased until the resting pulse rate is lowered to about 60/minute and the angina is relieved with-

out the development of congestive cardiac failure. Weight gain is a useful early indicator of the latter. The average, effective, daily dose of propranolol is about 100-200 mg. But some patients may require as much as 480 mg. per day. Propranolol is not particularly effective against angina at rest or on minimal exercise since its beneficial effect in the absence of sympathetic stimulation is small. In general, long term treatment with propranolol is safe and prognosis is better in those who respond than in those who do not. In patients with chronic, obstructive, lung disease, a selective beta-blocker such as metoprolol (50 mg 2-4 times a day) can be used in place of propranolol.

(3) *Calcium channel blockers*: Variant angina is generally relieved rapidly by nitroglycerine. Calcium antagonists are invaluable in the prophylaxis of such attacks. Nifedipine and verapamil are equally effective in this respect and the choice between them rests on other factors already discussed. Propranolol alone is not effective in these patients but can be usefully combined with nitrates.

In patients with angina of effort, these drugs appear to be as effective as betablockers as prophylactic agents. Further, they can be used in patients with chronic obstructive lung disease who cannot tolerate the beta-blockers.

In patients with stable angina, the dose of nifedipine needs to be titrated very finely. If a patient is benefited by 10 mg tid, he is likely to deteriorate on a higher dose. Nifedipine does not seem to have any beneficial effect in acute myocardial infarction.

In both angina of effort and variant angina, calcium channel blockers are commonly combined with nitrates.

(4) *Combination of a betablocker and a calcium channel blocker*: Such a combination produces a synergistic effect. Combination of verapamil and a beta blocker is more potent but combination of nifedipine and a beta blocker is safer. It can be used in patients with angina resistant to treatment with either drug alone and in patients with unstable angina.

(5) *Digitalis* is helpful in treating the syn-

drome 'nocturnal angina' which is an expression of left ventricular failure. Its use along with beta-blockers has already been discussed.

(6) *Advice about the way of life*: Excitement and emotional upsets are known to precipitate anginal attacks in susceptible individuals. A patient who suspects that he has 'heart pain', is usually very much worried and reassurance by the doctor would give marked relief in his symptoms. Rest, choice of occupation not involving manual work and occasional use of sedatives or tranquillizers form an important part of the antianginal therapy. In fact, the value of such an approach to the patient is far more than that of any known drugs. It has been demonstrated by controlled trials, that any inert placebo can diminish the severity of the symptoms in many patients; hence, one should be careful in accepting a well advertised antianginal drug which has helped "many" patients.

Alcohol has been advocated in the prophylactic therapy of angina pectoris. Experimentally, ethyl alcohol is not a coronary vasodilator. By removing the higher inhibitory controls in the central nervous system it may induce an individual to ignore the anginal pain. This might lead to more exertion and an aggravation of the myocardial ischemia. It does not prevent the electrocardiographic changes observed during exercise in anginal patients. A further disadvantage is the liberation of catecholamines by acetaldehyde, a metabolite of alcohol.

The false sense of security produced by alcohol may prove dangerous. Further, alcohol has been shown to have a negative inotropic action on the heart damaged by coronary artery disease. However, in alcohol addicts with angina, where the withdrawal of alcohol itself may precipitate undesirable effects, small amounts of alcohol may be permitted.

Anginal patients must be advised to give up smoking as it increases the heart rate and oxygen consumption of the myocardium. Further, absorption of carbon monoxide from the inhaled smoke increases the concentration of carboxyhemoglobin; this reduces the oxygen carrying ca-

capacity of blood.

The patient should be advised to avoid over-eating, exercise after eating, and extremes of heat, cold and humidity. He should avoid any type, amount or pace of activity known to precipitate angina in him; if it is unavoidable he should use NTG or isosorbide dinitrate sublingually 10-15 minutes before commencing the activity.

(7) *Treatment of associated diseases:* Weight reduction in obese patients and treatment of associated anemia, hypertension or thyrotoxicosis help in chronic prophylaxis of angina. Vasodilator antihypertensive drugs can aggravate angina by causing tachycardia but this can be countered by the concurrent use of a beta-blocker. Surgical treatment of aortic valvular disease and aorto-coronary bypass in selected patients with blocked coronary arteries have given encouraging results.

(8) *Supervised, graded, exercise training* improves exercise tolerance in anginal patients probably by increasing oxygen extraction in the peripheral circulation. This allows more physical activity to be undertaken with relatively less increase in heart rate and in cardiac output. The work load on the heart is thus kept below the angina index. Isometric physical activity of any type is, however, harmful in such patients and should be avoided.

Variant angina of Prinzmetal: The treatment of this condition has already been discussed.

Unstable angina: This condition requires aggressive medical treatment, preferably in a coronary care unit. The patient is treated with complete bed rest, large doses of nitrates orally or sublingually, calcium antagonists, and doses of a beta-blocker sufficient to lower the heart rate to 50-60/minute. In resistant cases, intravenous nitroglycerine is useful.

Requirements of an ideal antianginal agent:

(1) It should selectively dilate the coronary arteries without producing significant alteration in blood vessels.

(2) Cardiac output, blood pressure, pulse rate and oxygen consumption of the myocardium

should remain unchanged.

(3) It should protect the heart from the stress-induced adrenergic effects.

(4) It should act rapidly, should have sufficient duration of action, should not produce tolerance and should be harmless.

None of the available antianginal agents satisfies all these requirements.

DRUGS USED IN THE TREATMENT OF PERIPHERAL VASCULAR DISORDERS

Vasodilator drugs have been frequently advocated for the treatment of peripheral vascular diseases. The experience with these drugs, however, is disappointing. There is still no single effective measure for treating occlusive arterial diseases. The major difficulty encountered in the systemic administration of vasodilator drugs is their inability to produce selective vasodilatation in ischemic areas. This is particularly hazardous in cases of unilateral occlusive disease in which generalized vasodilatation aggravates ischemia by shunting blood from the ischemic extremity to the normal extremities. The effect can be confined to a specific vascular bed, however, by the intra-arterial injection of some of the vasodilator agents.

Vasodilator drugs often produce beneficial results in Raynaud's disease and in acrocyanosis. They are notoriously ineffective in intermittent claudication. Proper prophylactic care of ischemic extremities is vastly more important than the use of vasodilator drugs in the medical management of organic occlusive arterial disease.

The principles of treatment are :

(a) To correct the underlying disorder such as anemia, diabetes or polycythemia vera.

(b) To increase the local circulation by such means as postural exercises.

(c) To take proper precautions against cold.

(d) To avoid such factors which precipitate vasospasm e.g. smoking.

(e) Maintenance of local hygiene, avoidance of trauma and prompt treatment of infection, if present.

(f) Drug therapy.

The drugs used in the treatment of peripheral vascular disorders are:

(1) *Beta adrenergic stimulants*: Nylidrin and isoxsuprine (see Chapter 14).

(2) *Alpha adrenergic blocking agents*: Phe-

noxybenzamine, tolazoline and azapetine, discussed in Chapter 14.

(3) *Anticoagulants*: Heparin and coumarin derivatives, discussed in Chapter 29.

(4) *Miscellaneous agents*, e.g. Nicotinic acid cyclandelate, pentoxifylline (see Chapter 29).

28 Pharmacotherapy of Shock

Shock may be defined as a state of acute systemic circulatory failure associated with underperfusion of tissues, which is incompatible with life if untreated and persisting for more than a short time. It may be initiated by trauma, acute blood loss, depletion of body fluids, severe infection or acute myocardial dysfunction. In those conditions, it may be mediated by one or more of the following mechanisms; of these, hypovolemia is the most important one.

(1) *Hypovolemia*: This may be defined as a reduction in the circulating blood volume and can arise in many different ways. When present, it evokes, through the baroreceptors, a generalized, compensatory sympathoadrenal discharge and peripheral vasoconstriction. This latter is responsible for many of the clinical manifestations of shock. Though it helps to maintain the cardiac output and is important in short-term survival, it aggravates the hypovolemia by making the microcirculation very sluggish and thus reducing the effective intravascular volume.

As a result of the excessive sympathoadrenal discharge, a redistribution of the cardiac output occurs with reduction in the blood flow to the skin, the intestines and the kidneys. The blood pressure is stabilized but the tissue perfusion is impaired. Excessive vasoconstriction results in slowing of the blood flow, local hemoconcentration from loss of fluid from the capillaries into the tissues and in local formation of thrombi in the microcirculation. This causes tissue hypoxia which may lead to acidosis and to liberation of several substances such as histamine, kinins, prostaglandins and cardiodepressant peptides into circulation. Tissue hypoxia damages intracellular organelles such as lysosomes with liberation of enzymes which destroy the other intracellular structures. The coronary filling is mainly

diastolic and excessive fall in diastolic blood pressure (together with cardiodepressant peptides) adds a cardiogenic element to any other variety of shock. Inadequate cerebral blood flow leads to mental changes. Microcirculatory changes in the lungs lead to pulmonary odema (shock lung); this is abetted by neurogenic and mechanical factors which lead to ventilatory failure and by respiratory infection. Oligemic acute kidney shut down completes the devastating picture.

(2) *Failure of the heart* as a pump as in acute myocardial infarction.

(3) In *shock due to sepsis* and burns, the peripheral resistance is low (warm shock); the cardiac output is elevated initially but is maldistributed exactly as in shock with low cardiac output, with all the disastrous consequences detailed above. Moreover, the hypoxia is aggravated in septic shock (a) by fever which increases the oxygen requirement and (b) by greater affinity of hemoglobin for oxygen. In the later stages, the cardiac output falls and the peripheral resistance rises markedly.

(4) Rarely, shock may be produced by a complete failure of the compensatory sympathoadrenal discharge to occur, as in some cases of acute myocardial infarction.

The clinical picture of shock is variable but generally consists of pallor, sweating, cold extremities, rapid and thready pulse and air hunger, all due to the sympatho-adrenal discharge. Cyanosis of the extremities may or may not be seen. Rarely, the extremities may be warm (even in the absence of fever) whereas the circulation to the vital organs may be critically compromised. Oliguria (urine output less than 30 ml per hour), mental changes (somnolence, confusion, restlessness), acidosis and a marked difference in the

temperature between the rectum and the skin are all indicators of reduced cardiac output and reduced tissue perfusion. Central venous pressure (CVP) is the best guide to hypovolemia. If it is low to begin with and fails to rise during intravenous infusion of fluid at the rate of 10-20 ml per minute for 10-15 minutes, hypovolemia can be diagnosed. If during such infusion, the CVP exceeds 15 cm of water or rises more than 5 cm of water over the basal level, pump failure is a major component of the shock. In patients with chronic lung disease and after acute myocardial infarction, CVP does not truthfully reflect left ventricular filling pressure. In such patients monitoring of pulmonary artery occlusive pressure (PAOP) has been recommended as a better index of left ventricular filling pressure.

In the initial stages of shock, the blood pressure may be maintained by compensatory vasoconstriction. Later, a marked fall in the systemic arterial pressure is the rule. By the time the blood pressure falls, there is already a 25% deficit in the effective intravascular volume and hence an attempt should be made to diagnose and treat shock before the blood pressure falls significantly. The femoral pulses may be the best guide to the level of arterial pressure, since they are weak in hypotension but bounding in the presence of peripheral vasoconstriction with adequate arterial pressure. On the other hand, thready or absent radial or brachial pulses may be due to either severe hypotension or to reduction in extremity blood flow due to peripheral vasoconstriction. A low blood pressure recorded by means of a blood pressure cuff has the same significance as weak brachial or radial pulses.

Arterial hypoxemia (reduced PaO_2) and acidosis are the biochemical reflections of severe tissue hypoxia. It is customary to talk about 'irreversible' shock when the latter does not respond easily to treatment. It may be better to give up this term which admits defeat and call it 'refractory'.

Successful management of circulatory failure aims at (1) rapid recognition of the shock state;

(2) correction of the initiating insult (defibrillation, antibiotics, hemostasis etc.); (3) correction of secondary consequences of shock (e.g. acidosis, hypoxemia); (4) maintenance of function of vital organ (eg. cardiac output, B.P., urine output); and (5) identification and correction of aggravating factors. All the five items must be handled simultaneously.

Hemodynamic and biochemical monitoring of the patient's response to treatment is critical to success of the treatment. Heart rate, respiratory rate, systemic blood pressure, central venous pressure, mental state, urine output, electrocardiogram and arterial blood gases - all need repeated monitoring. In general, the metabolic parameters (mental state, urine output and blood gases) are likely to return to normal earlier than the hemodynamic parameters.

Although the specific treatment of shock depends on knowledge of its etiology, most studies have emphasized the importance of the reduced blood volume in the pathogenesis of the shock. Hence, it is vital to restore the intravascular blood volume as quickly as possible and that is the only treatment necessary in the many, except in shock due to myocardial infarction where the function of the heart itself is impaired. To be effective and safe, fluid administration should be monitored by measurement of central venous pressure (CVP) and arterial blood pressure. Rise in CVP without a corresponding rise in arterial blood pressure during intravenous fluid therapy denotes an overloading of the circulation. To avoid such overloading, keep the CVP below 15 cm of water.

Various types of fluids used for volume replacement are:

I. Whole blood and plasma.

II. Colloidal plasma substitutes: Dextran, hydroxyethyl starches, polyvinylpyrrolidone and oxypolygelatin.

III. Crystalloid plasma substitutes: Normal sodium chloride solution and dextrose solution.

I WHOLE BLOOD AND PLASMA: Whole

blood, obtained from human donors by aseptic technic, is preserved with A.C.D. solution containing 2.5 g. of disodium monohydrogen citrate and 3.9 g. of dextrose in 120 ml. This quantity of anticoagulant solution is utilised for preservation of 420 ml. of blood.

Blood is stored at a constant temperature varying between 2°C to 6°C; storage of blood below 2°C damages the red blood corpuscles. Blood stored in this fashion must be utilised within a period of 21 days, after which it deteriorates.

It is vital to maintain the temperature constantly below 6°C. This prevents the multiplication of bacterial contaminants. However, some bacilli can multiply at a temperature below 6°C if they have previously been stimulated by exposure to a higher temperature. As the degree of hemolysis produced by such organisms is too insignificant for detection, a bottle once taken out from the refrigerator and exposed to room temperature for a period of 30 minutes or more should not be replaced back for subsequent use but should be discarded.

The supernatant straw colour of the plasma serves as a convenient indicator to judge the suitability of blood sample for use. Pink or red stained plasma indicates hemolysis due to bacterial contamination.

Blood should not be used after 3 weeks as the fragility of the erythrocyte is increased after this period. Supernatant plasma, however, is stable and can be used instead.

In the absence of an unusual hemolytic state or factor, the transfused erythrocyte has an average life of 4 months.

Rh positive blood should not be given to Rh negative individual if it can be avoided; at least, it should not be repeated in a Rh negative individual who has received Rh positive blood transfusion previously.

Indications for blood transfusion:

(i) **Acute haemorrhage:** Before starting blood transfusion, an attempt should be made to

assess the degree of blood loss. This can be done conveniently if the bleeding is external as in case of external injuries or gynaecological emergencies. Many times, however, one has to rely mainly on clinical signs and symptoms such as pallor, tachycardia and hypotension to gauge the degree of blood loss.

If the systolic blood pressure has reached 80 mm. Hg. or is rapidly falling below that level, transfusion of O group blood, preferably Rh negative, should be started immediately. It should be given rapidly to start with and later the rate should be adjusted to 40 drops per minute. If restoration of circulating blood volume is not carried out without delay, irreversible damage may be inflicted on the vital organs like the brain and the kidneys because of hypoxia.

Adequacy of transfusion can be judged from the reappearance of colour and warmth in the patient, filling of veins and the improvement in pulse and blood pressure.

(ii) **Anemia:** Blood transfusion is indicated in:

(a) Severe anemia with haemoglobin below 20 per cent (2.9 g.%).

(b) Aplastic and refractory anemias.

(c) Haemolytic anemias.

(d) Cases of dyshaemopoiesis.

(e) As a pre-operative measure.

Ten ml. of whole blood per kilogram raise the haemoglobin level by 1 gm per cent. Children with weight less than 25 kg. should be given 20 ml./kg. of blood and premature infants 10 ml./kg.

In chronic severe anemia and in sepsis, the myocardium is on the verge of ischaemia and transfusion must be administered with utmost caution. The rate should not be allowed to exceed 10-15 drops per minute. Failure to observe this precaution may result in the development of cardiac failure.

(iii) **Other haematological disorders:**

In this case blood transfusion is given:

(a) to provide clotting factors and platelets and

(b) to provide leucocytes in cases of agranulocytosis. Fresh blood is preferred as the leucocytes deteriorate on storage.

(iv) **Miscellaneous:**

(a) Supply of antibodies in severe infections.

(b) Protein deficiency.

(c) Exsanguination transfusion with withdrawal of the patient's blood and simultaneous replacement with donor's blood. This can be life-saving in kernicterus in the newborn. It has also been used with success in hepatic coma due to acute infective hepatitis.

(d) Intrauterine transfusion: Transfusion of fresh blood in the Rh positive foetus of a Rh negative mother has been achieved in utero. It has given encouraging results in reducing the mortality due to erythroblastosis foetalis.

Complications of blood transfusion:

(a) *Pyrexial reaction*: Rigor, a common manifestation, is mainly due to imperfect sterilization of the apparatus. In the event of a rigor the transfusion should be stopped. The patient is covered with blankets. In severe cases morphine, anti-histaminics and glucocorticoids are employed. Usually it is due to pyrogen but occasionally it can be an early manifestation of a more serious reaction, especially hemolytic transfusion reaction.

(b) *Allergy*: Antihistaminics and adrenaline are used to treat this manifestation. It is better to enquire about previous history of urticaria in the donor to prevent this effect.

(c) Air embolism.

(d) Myocardial failure due to hypervolemia and circulatory overload.

(e) *Transmission of disease*: (i) *Syphilis*. The *Treponema pallidum* does not survive refrigeration for more than three days. In an emergency prophylactic use of penicillin can prevent this complication. (ii) *Malaria*. (iii) *Acute viral hepatitis*. This is one of the most serious adverse reaction and presently there is no practical method of sterilizing blood. It appears that there are at least two different forms of viral hepatitis

caused by immunologically distinct viral agents. 'A' virus causes the disease with a short incubation period (infectious hepatitis) while 'B' virus causes serum hepatitis with a long incubation period. Hepatitis virus B is associated in many cases with hepatitis-associated antigen (HAA, Australia antigen) which can be detected. Further, a non A - non B type of viral hepatitis has been described after blood transfusion. (iv) *Acquired immunodeficiency syndrome (AIDS)*.

(f) *Haemolytic reaction* due to mismatched transfusion is characterised by rigor, pain in loins, jaundice, haemoglobinuria and oliguria. The treatment of an acute hemolytic reaction is aimed at prevention of acute renal shut down. Mannitol (20 g. 20%) should be administered rapidly, to initiate diuresis. If diuresis occurs, it should be maintained (at 100 ml/hour) by giving normal saline, by maintaining blood pressure (100 mm systolic) and by alkalinizing the urine with 40-50 mEq of sodium bicarbonate, given intravenously. If diuresis fails to occur, acute renal failure should be diagnosed and the patient treated accordingly.

(g) Citrate intoxication leading to cardiac irregularities and metabolic acidosis due to alkali depletion, is a rare complication seen only on massive blood transfusions (generally more than 5 units of blood). Other complications after massive blood transfusion are: pulmonary insufficiency with adult respiratory distress syndrome (due to debris comprising of platelets, leucocytes and fibrin, in the stored blood); hypothermia (if blood is transfused without warming it to body temperature); and hemorrhagic diathesis (due to dilution of platelets and clotting factors in patient's own blood or due to disseminated intravascular coagulation).

(h) Storing of blood at a temperature below 6°C causes an efflux of potassium from erythrocytes into the plasma. When the blood is brought back to room temperature, potassium re-enters the erythrocytes. Failure to re-warm the blood to room temperature may lead to hyperkalemia in the patient.

Packed red cells can be transfused when it is desired to increase the oxygen carrying capacity of blood without increasing its volume. A packed red cell preparation is made by removal of 40 per cent of the supernatant plasma. The red cell content of the remaining packed cells should be at least 5.5 million per cubic millimeter. Concentrated red cells have to be infused within twelve hours of preparation. Fifteen ml./kg. of red cells increase the haemoglobin level by 2 g per cent. The amount of packed cells administered should not exceed 500 ml. at a time. The amount administered in children under 25 kg. is usually 15 ml./kg. of body weight while 10 ml./kg. are administered in premature infants.

Plasma is used for infusion in oligemic shock, particularly in burns. It is available as citrated liquid plasma or as powdered plasma in a dry state; the latter is easier to store. Plasma is prepared by mixing equal parts of citrated whole blood from different persons and then separating plasma by centrifugation. Such pooled plasma should preferably be obtained from a small number of donors (less than 10-12), and to ensure cross-neutralization of the haemagglutinins, donors should be derived in fixed proportions from the different blood groups. Strict aseptic precautions must be observed during processing of plasma preparations. In the preparation of citrated liquid plasma, unstable proteins such as fibrinogen are removed by adsorption on kaolin. The final product thus contains only the stable proteins (albumin and globulins). The total protein content is 4.5 per cent. Citrated plasma can be utilised for a period of 2 years after its preparation.

The dried plasma prepared by freeze drying is stored in sterile sealed containers in an atmosphere of nitrogen. The total protein content of dried plasma, when reconstituted, is 4.5 per cent. It contains significant amounts of fibrinogen. In the dry state, it remains stable for a period of 5 years.

In the preparation of these plasmas, the labile

constituents of the coagulation system are destroyed and hence, these preparations are of little value in the treatment of haemorrhagic states. The coagulation components, however, can be supplied from fresh frozen plasma. Hence the plasma, separated immediately after withdrawal of blood, is quickly frozen at -20°C and is subsequently stored at this temperature. Gentle thawing is carried out before use.

NORMAL HUMAN SERUM ALBUMIN: This sterile preparation is obtained from human whole blood. It is used to reduce edema and to raise the serum protein level in hypoproteinemia, in hypovolemic shock and in solution as a vehicle for transfusing packed red cells. It is usually non-toxic and does not interfere with normal coagulation mechanisms. It is given as 5% or 25% solution. The 5% solution is given undiluted usually at a rate of 2 to 4 ml./min. The 25% solution can be administered undiluted or diluted with sterile saline or 5% dextrose. Undiluted solution is used in the presence of edema. In patients with low cardiac reserve the rate of administration should be slow 1 mg/min.

Various other plasma fractions separated chemically under controlled conditions have found therapeutic applications. Thus, human gamma globulin injection is employed in the prevention or attenuation of certain infectious diseases like measles, while fibrinogen is used in the treatment of afibrinogenaemia. Preparations like human and bovine thrombin and human fibrin foam are discussed elsewhere.

II. Colloids: In the treatment of oligemic shock, it is vital and often life-saving to correct the circulatory fluid volume and both plasma and blood may not be available immediately. This has necessitated the search for artificial colloids for volume replacement. The plasma expanders are substances of relatively high molecular weight, which when infused into the blood stream, remain there long enough to augment the volume of the circulating fluid by increasing the oncotic

pressure.

Requirements of an ideal plasma expander:

(a) It should have an oncotic pressure comparable to that of plasma.

(b) It should remain in the circulation for an adequate period to perform its function and yet be eventually disposed of either by metabolic degradation or by excretion.

(c) It should not affect any visceral function adversely and should not have antigenic, allergenic or pyrogenic effects.

(d) It should not interfere with blood grouping or cross-matching, and should be compatible with other intravenous fluids and drugs.

(e) It should remain stable over a long period of storage and at usual variations in environmental temperature. It should be easily sterilized and have a viscosity suitable for infusion.

(f) It should be cheap and easily available.

The compounds used as plasma expanders are:

DEXTRAN: Dextran was originally isolated from beet sugar, where it is formed by the action of a contaminating bacterium *Leuconstec mesenteroides*. Native dextran has a very high molecular weight (40 million) and from it can be prepared low molecular weight dextrans. Those used in therapeutics are Dextran 70 (Macrodex, M.W. 70,000) and Dextran 40 (Lomodex, M.W. 40,000). Dextran 70 is available as a 6% solution and Dextran 40 as a 10% solution, in either isotonic saline or 5 percent dextrose. They are infused intravenously in the dose of 10 ml per kg. body weight in the treatment of shock.

The oncotic pressure of dextrans is similar to that of plasma proteins and they persist in the plasma with an effective half life of about 24 hours. Animal experiments indicate that 1 g of dextran in circulation maintains about 20 ml of plasma volume as compared to 1 g of albumin which maintains about 12 ml. While infusing the dextrans, care should be taken not to overload the circulation for fear of precipitating cardiac failure. The dextrans also inhibit rouleaux for-

mation by R.B.Cs. and have an antisludging effect on blood; they are claimed to improve the microcirculation independently of simple volume expansion. They may not interfere with typing, crossmatching or Rh determination. However, they coat the platelets and coagulation factors and interfere with their function. In large doses, dextrans can cause widespread hemorrhages.

Dextran 70 tends to be retained in the body especially in the liver and the reticuloendothelial system. Dextran 40 is rapidly excreted by the kidneys; as much as 50 per cent is excreted in 24 hours and the remainder in 4-7 days. Dextran molecules not excreted from the body are slowly oxidized over a period of weeks.

Dextrans are potent antigens especially when administered in small doses by the subcutaneous route. However, administration of massive doses intravenously does not induce antibody formation, probably because of immunological paralysis. Allergic reactions including fatal shock are seen in about 10 per cent of persons to whom it is administered, including those who have never received it in the past. Those allergic to dextran continue to remain so in future.

During its excretion through the renal tubules, dextran 40 can clog the tubules and is known to occasionally precipitate acute oliguric renal failure which is gradual in onset (3-6 days) and hence may be initially missed. The following precautions should be taken to guard against this possibility: (1) Do not infuse more than 1 litre (20 ml./kg.) per day. (2) Do not give it if the urine output is less than 1500 ml per day or the blood urea is 60 mg. per cent or higher. (3) Do not give any more if the urine output drops or the specific gravity of the urine rises above 1045 during its administration; in such cases, try to maintain a high urine output by using diuretics and a high fluid intake. (4) Do not use dextran for more than 5 days.

Dextrans are probably almost ideal plasma expanders. They can be easily sterilized by either filtration or autoclaving. They can be stored

without any special precautions for upto 10 years and thus can be stockpiled for emergency use.

They are contraindicated in those who are known to be allergic to them; in patients in cardiac failure; in existing or threatened acute oliguric renal failure; and in patients with hypofibrinogenemia or marked thrombocytopenia.

HYDROXYETHYL STARCHES: Addition of hydroxyethyl groups to starch molecules makes them resistant to hydrolysis by amylase and prolongs their intravascular half-life. One preparation (Hetastarch, M.W. 450,000) of hydroxyethyl starch has been extensively tried in treating shock. Compared to dextrans, hetastarch (a) maintains blood volume longer, (b) is non-allergenic and (c) does not cause acute renal failure or coagulation disturbances.

POLYVINYLPYRROLIDONE: This is a synthetic, water soluble, hydrophilic polymer of heterogenous molecular sizes with an average molecular weight between 35,000 and 40,000.

It is administered intravenously, as a clear, amber-coloured, sterile, 40 per cent solution in buffered physiological saline.

It has the capacity to bind drugs like penicillin and insulin and a tendency to produce agglutination of erythrocytes. Hence, it interferes with blood grouping and also produces a rise in sedimentation rate for 24 hours following its administration. The compound has been demonstrated in the Kupffer cells of the liver many months after its administration. In rats, it has been found to produce reticulum-cell sarcoma but no such adverse effect has been reported in man.

Much of the polyvinylpyrrolidone is rapidly excreted; 50 to 75 per cent of the administered dose is recovered from the urine within 46 to 72 hours. About 10 per cent is excreted in bile. The remainder (fractions of large molecular weight; above 120,000) is not metabolised and is apparently stored indefinitely in the skin, skeletal muscle and the reticuloendothelial system. It may interfere with antibody formation.

GELATIN POLYMERS: Various gelatin polymers have been investigated as plasma substitutes. One such polymer of degraded gelatin available commercially (Haemaccel) is a polypeptide with molecular weight of about 30,000-35,000. It is dissolved in an electrolyte solution with the final pH of the infusion between 7.2-7.3. In this state it can remain stable for 3 years at room temperature. Given intravenously, its mean serum half life is 4 to 5 hours. Approximately 60-80 per cent of the gelatin is excreted unchanged by the kidneys. It is claimed that the preparation exerts osmotic activity similar to that of albumin. It does not interfere with coagulation, blood grouping and cross matching and is non-antigenic. Occasionally, it may cause flushing, urticaria and rigors. Bronchospasm and fall in blood pressure can also occur. It is available as 3.5 per cent gelatin polymer in 500 ml. infusion solution.

III. Crystalloid fluids:

(a) **NORMAL SALINE**, 0.9 per cent, is the most widely used intravenous preparation. It is mainly useful to replace lost sodium, chloride and water, particularly in cases of dehydration. It is commonly used as a vehicle for giving i.v. drugs by drip. It is important to note that noradrenaline is unstable at the neutral pH of normal saline but is stable at the acidic pH of dextrose solution. Though normal saline is adequate to raise the effective blood volume and blood pressure in emergencies, it leaves the blood rapidly and hence, has a very limited duration of effect. Too rapid an administration of large quantities of normal saline can produce pulmonary edema. The febrile reaction that sometimes occurs is usually due to the presence of pyrogens.

(b) **DEXTROSE** infusion as a 5 per cent solution is particularly useful when the kidney function is impaired. Further, it supplies nutrition. It has, however, similar disadvantages as normal saline.

In general, colloids are superior to crystalloids in maintaining blood volume and in minimizing

the shock level. But their cost puts a limit on their routine use in all shocked patients.

CARDIOVASCULAR DRUGS IN SHOCK:

The major cardiovascular drugs used are summarized in Table 28.1. The other vasopressors used are mephentermine, metaraminol, methoxamine and phenylephrine. Mephentermine acts chiefly by increasing the cardiac output. Metaraminol acts like noradrenaline but is less potent. As it acts by releasing NA from the nerve endings, prior treatment with reserpine (which depletes catecholamine stores) makes the patient resistant to this drug. Methoxamine and phenylephrine, being pure alpha adrenergic stimulants, are useful only in neurogenic shock. For doses of these three drugs, see Chapter 14. Correction of acidosis can restore sensitivity to the sympathetic

amine drugs.

Except as a desperate resuscitative measure, the use of vasopressor should be preceded by expansion of intravascular volume. The systolic blood pressure should be maintained around 90-100 mm Hg (or previously hypertensive patients, 30 mm Hg below the usual pressure) during vasopressor infusion, as at infusion rates needed to raise the pressure higher, peripheral resistance rises disproportionately and compromises tissue perfusion. Use of isoprenaline should be monitored by PAOP measurement and measurement of arterial blood pressure; heart rates over 120/minute are likely to be associated with cardiac arrhythmias and should be avoided. Isoprenaline should never be used in shock due to myocardial infarction.

Table 28.1: Properties of important cardiovascular drugs used in shock

	Dopamine*	Isoprenaline*	Noradrenaline*
Action	Low dose rates stimulate beta adrenergic and high dose rates stimulate alpha adrenergic receptors. Direct action on dopaminergic receptors dilates coronary, splanchnic and renal arteries.	Stimulates beta receptors	Stimulates mainly alpha receptors
Cardiac output	↑ With low dose rates	↑	May increase
Peripheral resistance	↓ With high dose rates	↓	↑
Urine output	Increases ++	Increases+	May increase
Infusion rate	2-15 µg/kg/min (low) 20-50 µg/kg/min (high)	Less than 10 µg/min	1-5 µg/min
Comments	Drug of choice after myocardial infarction. May be used in other types of shock.	Useful in later stages of endotoxic shock Cardiac action not inhibited by acidosis. Do not use in shock after myocardial infarction	General purpose vasopressor Action inhibited by acidosis

* Infused preferably in 5% dextrose in water.

TREATMENT OF SHOCK

Shock may be arbitrarily classified as :

I. Cardiogenic shock due to acute heart failure e.g. myocardial infarction, acute myocarditis or severe paroxysmal tachycardia.

II. Hypovolemic or oligemic shock due to acute loss of plasma or blood as in burns, haemorrhage; or due to dehydration and sodium depletion as in excessive vomiting and diarrhoea due to any cause, diabetic acidosis and Addison's disease.

III. Neurogenic shock due to pooling of blood in post-capillary capacitance blood vessels, e.g. shock encountered with spinal anaesthesia, spinal cord injury, abdominal and testicular trauma and perforation of a hollow viscus. In fact, it is a form of hypovolemic shock.

IV. Anaphylactic shock which is probably due to release of histamine and other substances like serotonin and bradykinin as a result of a reaction between the antigen and antibodies fixed to target tissues.

V. Bacteremic or endotoxic shock produced as a result of severe infection with gram negative bacteria like *E. coli*. Though sometimes termed as **endotoxin shock**, it is uncertain whether shock in these cases is due to the effects of endotoxin. Gram positive organisms, particularly resistant staphylococci, are also capable of producing shock.

VI. Haemo-obstructive shock produced as a result of obstruction of a main vascular channel, e.g. shock due to massive pulmonary embolism.

I. Shock due to myocardial infarction:

(a) **Relief of pain:** The intravenous administration of 2.5 to 5 mg. of morphine hydrochloride ensures a rapid relief from pain and thereby minimises the shock. Administration of morphine subcutaneously may be less useful in such cases because of peripheral circulatory collapse which delays its absorption. Morphine may be repeated, if necessary, after 30 minutes. Alternatively, pethidine hydrochloride 25 to 50 mg. may

be given by intravenous route particularly, in the presence of bradycardia. Both morphine and pethidine produce release of histamine and can produce dangerous hypotension. This can be corrected by elevating the lower limbs. Morphine may cause sinus bradycardia and respiratory depression. The incidence of vomiting is claimed to be more with pethidine than with morphine.

(b) **Oxygen and rest:** The patient should be confined to bed and allowed to breathe 100 per cent of oxygen by means of a face mask. Even a slight increase in activity could worsen the condition. In the presence of left ventricular failure, simultaneous use of digitalis and diuretics with oxygen is likely to be beneficial.

(c) **Maintenance of effective blood volume:** The effective circulating volume is reduced in cardiogenic shock. This should be corrected by:

(i) Elevating the lower limbs and thus increasing the venous return to the heart and,

(ii) Infusing 5 per cent dextrose. Excessive infusion, however, may cause pulmonary edema. This can be averted by a careful monitoring of CVP or PAOP and arterial blood pressure.

(d) **Vasopressors:** Dopamine and dobutamine are the vasopressor drugs of choice in this condition. If they are not available, NA may be used. *Isoprenaline is contraindicated in shock due to myocardial infarction.*

(e) **Treatment of arrhythmias:** Ventricular ectopic beats at a frequency of 5/min. herald the possibility of serious ventricular arrhythmia and should be treated with intravenous infusion of lignocaine, given at a rate of 1 to 2 mg./min., or with procainamide, 100 mg. intravenously every 5 minutes, to a total dose of not more than 1 gm. Alternatively, lignocaine may be given intramuscularly in the dose of 400 mg. and repeated if necessary. Ventricular tachycardia is a serious complication needing immediate therapy with i.v. infusion of lignocaine or D.C. Shock. Atrial fibrillation and flutter may need digitalization or D.C. Shock treatment. Sinus or nodal bradycardia is treated with i.v. atropine sulfate, 0.3 to 2 mg. or isoprenaline, 0.05 mg. intravenously.

Digitalis should be given if congestive cardiac failure develops.

Supplementary therapy in myocardial infarction :

(i) **Anticoagulants:** Anticoagulants are mainly used to prevent venous thrombosis. They are not of immediate value of cardiac infarction and need careful supervision. The maximum mortality with acute myocardial infarction is within first 48 hours after the attack and this is not influenced by anticoagulant therapy. The usefulness and limitations of anticoagulant therapy are discussed in Chapter 29.

(ii) **During recovery** easily digestible low residue diet and a lubricant purgative should be administered to prevent straining during defaecation.

(iii) Use of sedatives, tranquillizers and weight reduction can be beneficial.

II. Hypovolemic shock:

(a) Immediate treatment is directed towards restoration of effective blood volume by suitable fluids given intravenously. Hypovolemic shock is usually associated with metabolic acidosis as tissue hypoxia increases the production of lactic acid. This can be corrected by administration of a suitable alkali. Associated basic metabolic abnormality such as diabetes or Addison's disease must receive immediate treatment.

(b) Abnormalities of electrolyte balance should be corrected by administration of electrolytes.

(c) As soon as the clinical state of the patient permits, the causative factor should be corrected, if possible.

(d) Morphine should be administered intravenously to relieve pain if shock is not associated with head injury or suspected acute abdomen.

(e) Vasopressor agents may be employed to correct hypotension associated with hypovolemic shock. They reduce the capacity of the vascular system and increase the effective circulating blood volume. However, fluid deficit must be corrected before using vasopressors.

Without such correction, the use of vasopressor agents worsens the condition of the patient by reducing renal and cerebral blood flow and by increasing the oxygen consumption of the myocardium.

(f) Oxygen administration is helpful in patients with arterial hypoxemia.

III. Neurogenic shock: This shock should be treated on similar lines as hypovolemic shock. Use of vasopressor agents is definitely indicated here. Alternatively, 0.5 to 1 ml. of ephedrine hydrochloride solution containing 45 mg. of the drug per ml. may be injected prophylactically before administration of spinal anaesthesia.

IV. Anaphylactic shock: See Chapter 20.

V. Bacteremic shock (Endotoxin shock): Treatment of this form of shock comprises the use of an appropriate antibiotic, surgical intervention (if necessary), correction of acidosis, blood volume expansion, and therapy for hypotension.

VI. Haemo-obstructive shock should be treated on similar lines as cardiogenic shock.

Use of vasodilator agents in the treatment of shock: It is based on the concept that blood flow to certain critical areas, rather than blood pressure, is the important factor in survival from shock. The following evidence has been presented to support this concept.

(a) Clinical signs of shock such as pallor and sweating are also signs of vasoconstriction due to sympathetic overactivity.

(b) In experimental endotoxin shock in dogs, autopsy has revealed intense vasospasm in small arteries and veins in selected organs like lungs, kidneys and intestines with accompanying haemorrhagic necrosis of the small intestine. These responses are not commonly seen in man.

(c) Accentuation of shock in animals following administration of sympathomimetic amines, and

(d) A significant increase in survival rate of

animals following the procedures inducing vasodilatation e.g. sympathectomy or use of alpha adrenergic blocking agents.

On the basis of these findings, vasodilator drugs (phentolamine, sodium nitroprusside and nitroglycerine) have been used in treating certain forms of shock, especially cardiogenic shock. Such therapy can cause a dangerous fall in arterial blood pressure and hence in tissue perfusion, unless it is carefully monitored with PAOP as well as intra-arterial measurement of arterial pressure. Its use should be left to specialized units.

Use of corticosteroids in shock: Massive doses of corticosteroids (dexamethasone 3-5

mg./kg. I.V. as a bolus, followed by 1/10th this dose every 4-6 hours) have been advocated in the treatment of shock. The exact mechanism of their action is not known. A direct myocardial stimulant action and dilatation of the precapillary sphincter so as to increase tissue perfusion have been suggested as the important mechanisms. Experimentally, they have been found valuable in bacteremic shock. Their clinical usefulness, however, is controversial.

Recent data indicate that they do not provide any benefits in the treatment of severe sepsis and shock. In fact, resolution of secondary infection may be delayed in patients receiving glucocorticoids.

Section VIII: Drugs Acting on Blood and Blood Forming Organs

29 Drugs and Blood Coagulation

Drugs are used therapeutically to modify the processes of coagulation and thrombus formation. In principle, they can achieve this by acting at various stages of these processes: (a) platelet aggregation, (b) clot or fibrin formation, or (c) fibrinolysis. To understand the effects of these drugs, it is necessary to understand the mechanism of blood coagulation and thrombus formation.

Mechanism of thrombogenesis and blood coagulation: Hemostasis is the spontaneous arrest of bleeding from damaged blood vessels. When cut, the precapillary vessels constrict. Platelets adhere to the exposed collagen of the injured vessel (platelet adhesion). This causes them to release adenosine diphosphate which makes more platelets stick to each other (platelet aggregation), lose their individual membranes and form a viscous mass. This platelet plug stops the bleeding temporarily but for long term hemostasis it must be re-inforced by fibrin. The process of deposition of fibrin is called coagulation. Finally, local healing occurs by fibrosis.

Thrombogenesis is an abnormal state of hemostasis, leading to an intravascular thrombus formation. There are two types of thrombi: arterial (white thrombus) and venous (red thrombus). The process of formation of a white thrombus is merely an extension of the basic processes of platelet adhesion and platelet aggregation. The initiation of intravascular platelet adhesion is at the site of injury to or disease of the vessel wall. The arterial thrombus grows and may be sur-

rounded by a red thrombus and may occlude the artery or, by disintegrating, embolize the distal arterial tree. By contrast, a venous thrombus forms in an area of venous stasis (slow blood flow). It is largely a mass of fibrin with red cells entangled in its mesh and resembles a clot formed in a test tube.

Coagulation of blood comprises the formation of fibrin by a series of interactions among a large number of protein factors and other substances (Kallekrein, calcium, platelet factor) present in the plasma. *The clotting factors* (listed in Table 29.1) are proteins synthesized by the liver. Some of the factors (II or prothrombin; VII, IX and X) are vitamin K dependent for the final stage of their synthesis (carboxylation of glutamic acid residues) in the liver. In the process of clotting, each factor undergoes partial proteolysis to form an enzyme (activated factor labelled by the subscript 'a' after the Roman number indicating the factor e.g. Xa). The activated factor then brings about similar proteolysis of the next factor in the cascade of coagulation, leading ultimately to conversion of fibrinogen into soluble fibrin (friable clot) and finally, conversion of soluble fibrin into insoluble fibrin (firm clot). The other substances mentioned above aid the 'factors' in the process of coagulation. The coagulation proceeds along either *intrinsic system* or *extrinsic system*. All the reactants necessary for the intrinsic pathway (i.e. system) are already present in the blood in inactive form. The initiators of the extrinsic pathway (i.e. sys-

Table 29.1 : Blood Clotting Factors

Factor No.	Common name
I	Fibrinogen
II	Prothrombin
III	Thromboplastin
IV	Ionic calcium
V	Hereditary labile factor, Activator (AC) globulin, Proaccelerin.
VI	Accelerin, supposed to be active form of Factor V
VII	Proconvertin; Serum prothrombin conversion accelerator (SPCA)
VIII	Antihemophilic factor (AHF)
IX	Plasma thromboplastin component (PTC; Christmas factor)
X	Stuart-Prower factor
XI	Plasma thromboplastin antecedent (PTA)
XII	Hageman factor
XIII	Fibrin stabilizing factor, Fibrinase

tem) are not normally present in the blood; they are added by tissue injury. The two pathways have the common object of generating factor Xa from factor X. The intrinsic pathway is a slow pathway and minutes are required for the formation of activated factor X (factor Xa); by contrast factor Xa is generated within seconds by the extrinsic pathway.

In the normal circulation, the blood is kept fluid by several processes. Rapid flow of blood keeps the local concentration of clotting factors low. Antithrombin III, which is present in the blood, combines with and inactivates all the factors of the intrinsic pathway as well as any thrombin formed in the circulation. Any minute quantity of fibrin that may be found is removed by fibrinolysis (see later).

Patients who develop venous thrombosis seem to have three abnormalities: stasis within the venous system; some injury to or disease of the vessel wall; and a hypercoagulable state. This latter cannot be identified by the routine coagulation tests but has been defined by means of more advanced assays of the clotting factors.

Figure 29.1 depicts the current concept of the sequence in which the various clotting factors are 'activated' leading to the formation of a clot. The initiating event in both intrinsic and extrinsic systems appears to be 'contact' activation of factor XII and its conversion to factor XIIa.

DRUGS MODIFYING PLATELET FUNCTION

It is generally believed that intravascular

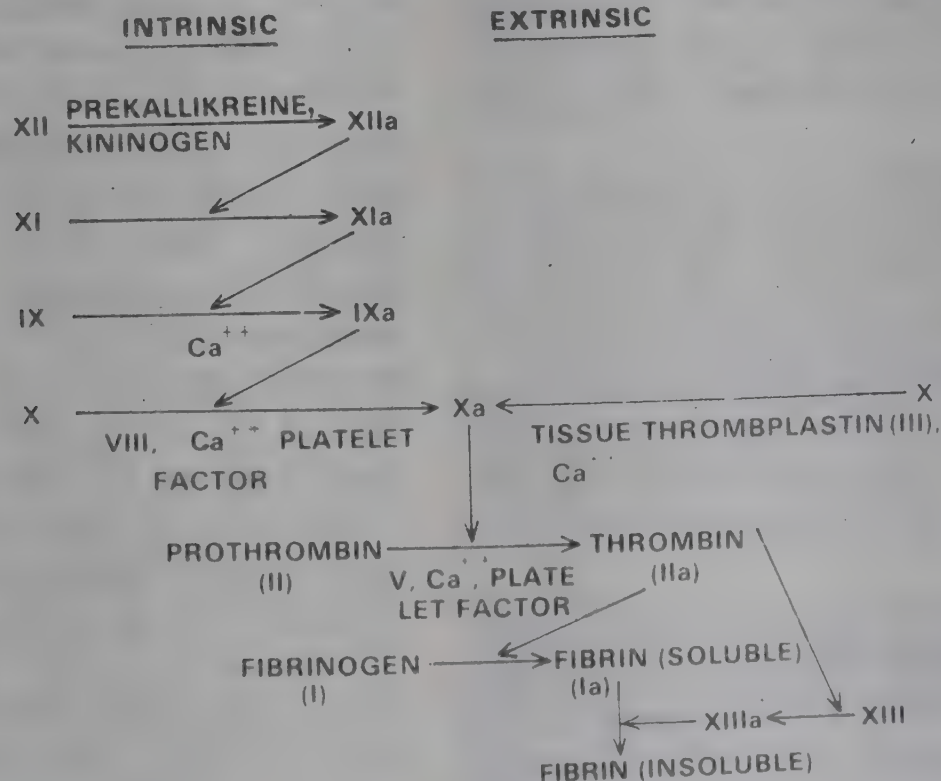


Fig. 29. 1: Mechanism of blood clotting

thrombosis is initiated by platelet adhesion and aggregation and is completed by the formation of fibrin. As a result of adhesion of platelets to the damaged vascular wall, adenosine diphosphate (ADP) is released which causes the aggregation of platelets. Hence, drugs interfering with the platelet aggregation may be useful in the prevention and treatment of thrombosis. Experimentally, various drugs such as aspirin, sulfinpyrazone (a uricosuric drug), dipyridamole (a coronary vasodilator) and dextran 40 (a plasma expander) have been shown to interfere with the aggregation of platelets; some of these like aspirin (150-300 mg. daily) and dipyridamole (100-300 mg. daily) have been tried clinically in the prophylaxis and treatment of intravascular thrombosis with beneficial results. Present data indicate that aspirin 150-300 mg. daily is useful in preventing reinfarction in patients with myocardial infarction and ischaemic heart disease as well as stroke in subjects with cerebrovascular disease (see Chapter 9). It should be started immediately.

Prostacyclin (PGI_2) is a naturally occurring potent vasodilator, and an inhibitor of platelet aggregation. It is produced by the walls of blood vessels. It is also present in other tissues such as the brain, the gut and the kidney. It is formed from PG-endoperoxide through the action of the enzyme prostacyclin synthetase. (See Chapter 21.)

Prostacyclin inhibits platelet aggregation by stimulating adenylate cyclase, leading to an increase in cyclic AMP levels in the platelets. In man, prostacyclin infusion, in addition to inhibiting platelets, causes vasodilatation, resulting in hypotension, tachycardia, headache and intense facial flushing. It causes renin release. The compound is very unstable and has a short half life of 3 minutes.

Prostacyclin and thromboxane A_2 (TXA_2) are both derivatives of arachidonic acid. But unlike PGI_2 , TXA_2 is mainly generated by platelets, is a potent vasoconstrictor and promotes platelet aggregation. Aspirin is highly active against

platelet cyclo-oxygenase. However, this enzyme of vessel walls is less sensitive to aspirin than is that of platelets. Hence, small doses of aspirin inhibit the synthesis of TXA_2 by platelets but higher doses also inhibit prostacyclin formation in the vessel walls as well. It has been suggested that a balance between TXA_2 and PGI_2 formation regulates platelet cyclic AMP *in vivo* and, therefore platelet aggregability. Lungs seem to synthesize fairly large quantities of prostacyclin and it could be that prostacyclin is a circulating hormone, playing an important role in the natural resistance of the organism against intra-arterial thrombosis. Prostacyclin potentiates the effect of heparin.

Various PGI_2 analogues are now being investigated for their possible therapeutic use in vascular diseases.

DAZOXIBEN is a substituted imidazole which selectively blocks production of TXA_2 . The compound is effective orally and is under evaluation.

DIPYRIDAMOLE (Persantin): This drug, introduced as a coronary vasodilator, has been shown to block the platelet phosphodiesterase enzyme. Its analogues potentiate the increase in cyclic AMP and platelet inhibition caused by the vessel wall prostacyclin. It has only a weak effect on *in vitro* platelet aggregation and hence, its action is possibly exerted on the vessel wall platelets rather than on the circulating platelets. The combination of vasodilator effect and vessel wall platelet interaction may explain the beneficial effect of this drug. It is used in the dose of 50-100 mg. three times a day, before food, in patients with transient ischemic attacks.

The drug may sometimes cause allergic reactions, headache and epigastric discomfort. It can be combined with aspirin or anticoagulants.

Ticlopidine, a new synthetic inhibitor of platelet aggregation, alters the platelet membrane directly. Given orally 250 mg twice daily, it inhibits platelet aggregation induced by adeno-

sine diphosphate, collagen, adrenaline and PAF. It prolongs the bleeding time. It does not inhibit cyclo-oxygenase or cyclic AMP phosphodiesterase. Adverse effects include neutropenia, rash and diarrhoea. The drug is under evaluation.

Pentoxifylline (Trental) : This new drug, an analogue of xanthines, is claimed to increase the deformability of the red blood cells in circulation and thus improve the microcirculation. It has been claimed to be useful in patients with cerebrovascular disease, especially those getting transient ischemic attacks; in those with chronic occlusive peripheral arterial disease, and in those with ischemic ulcers on legs. The drug may reduce plasma fibrinogen level and inhibit platelet aggregation. It causes mild gastrointestinal upset and central nervous system adverse effects. It is available as 400 mg sustained release tablets. The dose is one tablet 2 - 3 times a day after food. The drug is under evaluation.

Anticoagulant drugs can be divided into:

I. *Those used for preventing clotting of blood inside the intact vasculature.*

(a) Rapidly acting e.g. heparin.

(b) Slow acting e.g. (i) Coumarin derivatives e.g. bishydroxycoumarin, ethyl biscoumacetate and warfarin sodium. (ii) Indandione derivatives e.g. phenindione.

II. *Those used to prevent clotting of blood in vitro.*

The division is necessarily arbitrary as certain drugs can be used both *in vivo* as well as *in vitro*.

FAST ACTING ANTICOAGULANTS

HEPARIN: Heparin was discovered in 1916 by McLean, a medical student. It is a naturally occurring substance found in association with lipoproteins in the metachromatically staining granules of mast cells. These cells are abundant in the liver (hence the name heparin), and in the lung. Commercial heparin is obtained from the lung and the intestinal mucosa of pigs and cattle. It is generally believed that heparin is the natu-

rally occurring anticoagulant responsible for fluidity of the blood in the intact vasculature.

Purified heparin preparations obtained from different animals have different activities. The method of bioassay of heparin depends upon the capacity of heparin to prevent clotting of sheep or cattle plasma under standardized conditions. This activity is compared with that of the standard heparin powder; 1 mg of dry material obtained from the cattle lung equals 120 U.S.P. units.

Heparin is a mucopolysaccharide composed of an unknown number of sulfated D-glucosamine and D-glucuronic acid units linked through an oxygen bridge. The content of esterified sulfuric acid is very high, and this makes heparin a strongly electro-negative compound. Heparin is thus the strongest acid occurring in the body. The anticoagulant activity is attributed to its strong electronegative charge, forming complexes with positively charged proteins. It is used as the sodium salt. Commercial preparations are a mixture of low (7000) and high (more than 25,000) molecular weight fractions.

Pharmacological actions of heparin:

(1) **Blood coagulation:** Heparin prevents the clotting of blood both *in vivo* and *in vitro*. It probably acts on all the three stages of coagulation.

The exact mechanism of its action is not known but the prevention of thrombin formation is of primary importance. Heparin does not block the synthesis of prothrombin and other clotting factors. It facilitates the formation of complexes of heparin cofactor anti-thrombin, which is the principle physiological inhibitor of thrombosis. Heparin thus prevents the formation of fibrin monomer and inhibits its polymerization.

Heparin administration in therapeutic doses prolongs the clotting time (2 to 2½ times the normal).

(2) **Heparin and lipoprotein lipase:** Heparin abolishes the cloudiness of the hyperlipemic plasma (Tyndall effect) within minutes after its administration. This action occurs in doses too

small to exert an anti-coagulant effect. It is attributed to clearing factor activated by heparin, believed to be an enzyme called lipoprotein lipase. Lipoprotein lipase has been shown to be distinct from both pancreatic lipase and plasma esterase. Clearing of plasma thus does not take place when heparin is added to blood *in vitro*.

(3) **Miscellaneous actions:** Heparin has been shown to inhibit aldosterone secretion.

Heparin is claimed to exert some anti-inflammatory activity.

Absorption, fate and excretion: Heparin is not effective orally, but is well absorbed after subcutaneous injection. The use of radioactive heparin has demonstrated that the mast cells take up heparin in their metachromatic granules. This suggests that the mast cells may act as a storage depot for exogenously administered heparin.

The onset of anticoagulant action with an intravenous dose is almost immediate and reaches peak within 5 to 10 minutes. The prolonged clotting time returns to normal within 2 to 4 hours. The aqueous preparation is, therefore, administered at 2 to 4 hourly interval. In general, the duration of anticoagulant activity of a dose of heparin increases with the size of the dose.

Heparin is metabolized mainly by a liver enzyme termed heparinase. Following intravenous administration, 25 to 50 per cent of a single dose of heparin may appear in the urine in active form. *Heparin does not cross the placental barrier and is not secreted in the milk.*

Adverse reactions:

(a) Allergic and anaphylactoid manifestations include asthma, urticaria, rhinitis, and fever. It is advisable to give a trial dose of 1000 units of heparin even though these reactions develop rarely.

(b) Excessive or injudicious use of heparin may produce hemorrhage from various sites such as peptic ulcer, kidneys and hemorrhoids, and may cause memarthrosis or wound hematoma. It is advisable to avoid aspirin and other drugs which interfere with platelet function during heparin therapy.

(c) **Thrombocytopenia:** Heparin causes transient, mild thrombocytopenia in 25% of patients and severe thrombocytopenia in a few. The mild reaction results from heparin induced platelet aggregation. The severe form, which occurs on 8th to 12th day of treatment, is due to the formation of heparin dependent antiplatelet antibodies; it can result in tolerance to the anti-coagulant action of heparin and recurrent thromboembolic disease and a platelet count as low as 5000/c mm. The thrombocytopenia improves after discontinuation of heparin. Such severe thrombocytopenia reportedly occurs more often with heparin prepared from bovine lung than from porcine intestine. It has been reported even during 'low dose' heparin therapy. Low molecular weight heparins reportedly interact less readily with platelets than the high molecular weight heparins.

(d) Some patients develop transient alopecia after prolonged heparin therapy. Diarrhoea has been occasionally noted.

(e) Use of heparin in the dose of 15,000 units daily for a period of 6 months or more has been reported to cause osteoporosis and spontaneous fractures of ribs and vertebrae.

Preparations and dosage:

Heparin is available as sodium or calcium heparin. Since the commercial preparations of heparin vary in their potency ranging from 120 - 190 units/mg., the dosage of heparin must be prescribed in units.

(i) **I.V. infusion:** Initially, 5000 to 10,000 u into the tubing of infusion, followed by 20,000 to 30,000 u daily at the rate of 0.5 u/kg/min (1000 u/hour in a 70 kg man) in isotonic saline.

(ii) **I.V. Intermittent:** 10,000 u initially (in a 70 kg man) followed by 5000 to 10,000 u every 4 - 5 hours. In children, the dose is 50 - 100 u/kg initially, followed by a similar dose every 4 hours.

(iii) **Low dose, subcutaneous:** For prophylaxis, 5,000 u given every 8 - 12 hours, starting 1-2 hours before the operation and continuing till the patient is discharged. Injection is given with a small needle and the smallest possible volume

is employed, to prevent local hematoma.

Heparin should not be used intramuscularly.

Heparin therapy can be monitored by whole blood clotting time (Lee-White) which should be kept at 2 - 3 times the normal, and by activated partial thromboplastin time (APTT) which should be kept at $1\frac{1}{2}$ - 2 times the normal. Small doses of heparin given subcutaneously, for prophylactic use, do not require repeated monitoring of blood samples.

Heparin antagonists: The anticoagulant effects of heparin can be promptly arrested by the administration of strongly basic compounds which react with the strongly acidic groups of heparin, thereby abolishing the anticoagulant activity.

PROTAMINE SULFATE is the commonly employed heparin antagonist. The protamines are simple proteins with low molecular weight, found in the sperms of certain fish. Protamine sulfate is available as 1 per cent solution. It should be administered slowly, intravenously, not more than 50 mg. over a 10 minute period. one mg. of protamine sulfate neutralizes the anti-coagulant effect of 80-100 units of heparin activity. If more than 30 minutes have elapsed after heparin administration half of this dosage is required.

Protamine sulfate itself possesses anticoagulant activity. Because of this, it is considered unsafe to exceed the dose of 100 mg. over a short period. Intravenous injection of protamine may cause a sudden fall in blood pressure, bradycardia, dyspnoea, transitory flushing and a feeling of warmth. Protamine is thought to be nonantigenic.

SLOW ACTING ANTICOAGULANTS

These drugs are known as oral anticoagulants because, in contrast to heparin, they are effective by mouth.

COUMARIN DERIVATIVES : Bishydroxycoumarin or Dicoumarol, the first coumarin compound, was isolated from spoilt

sweet clover in 1943-1944 and was proved to be the causative factor in a cattle disease termed 'SweetClover Disease', characterised by a severe haemorrhagic tendency. Many chemically related compounds have been studied but only a few are clinically useful.

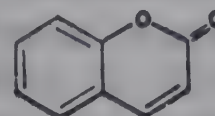


Fig. 29.2: Coumarin ring.

Pharmacological actions : The various coumarin drugs exert qualitatively similar pharmacological actions.

(1) **Blood coagulation :** Unlike heparin, coumarins have no anticoagulant action *in vitro*. The therapeutic action depends on the ability to prolong the prothrombin time by suppressing the synthesis of prothrombin and factors VII, IX and X by the liver, by competitive inhibition of vitamin K in the liver. Coumarin therapy is controlled by estimating prothrombin time of the blood. Bleeding time is unaltered.

(2) **Miscellaneous actions:** Coumarin therapy is found to increase the plasma anti-thrombin levels. Oral anticoagulants appear to reduce the incidence of spontaneous metastasis from malignant neoplasms. This effect seems to run parallel with the depression of prothrombin activity.

Both coumarin and indandione derivatives produce a uricosuric effect, by interfering with the renal tubular reabsorption of urate.

Absorption, fate and excretion: The absorption of coumarin compounds from the human gut is slow and incomplete. The drugs are extensively bound to plasma proteins. They cross the placental barrier and are also secreted in milk.

They are mainly metabolized in the liver. There is a considerable variation (as much as 14 fold) in the rate of detoxification in different individuals.

In contrast to heparin, there is a considerable lag (usually 24 to 48 hours) between the time of peak plasma level of coumarins and the therapeutic

tic response as measured by prothrombin time. This is because they prevent the formation of essential clotting factors by the liver and do not destroy the already circulating ones. It takes 5-7 days for prothrombin time to return to normal after cessation of therapy.

Adverse reactions: The incidence of haemorrhage has been reported to vary between 5 and 6 per cent; about 2% of these may be severe haemorrhages. There is no correlation between the onset of haemorrhage and the drug dose. Similarly, no correlation has been demonstrated between the occurrence of haemorrhage and the prothrombin, coagulation or bleeding time. In fact, controlled studies indicate that similar degree of hypoprothrombinemia may be found in patients on anticoagulants who bleed and those who do not.

The major and the most frequent haemorrhagic manifestation is haematuria, which is not fatal and does not lead to impairment of renal function. Epistaxis, bleeding gums, ecchymoses, haemoptysis and extensive uterine bleeding have been observed. Purpura is rare, but bleeding from an unsuspected peptic ulcer or neoplasm can often be fatal and sometimes the patient may come with symptoms of acute intestinal obstruction. Such patients are poor surgical risks and are usually treated conservatively.

The haemorrhage induced by coumarin compounds can be treated by large doses of vitamin K₁ oxide which enables the liver to synthesize the

clotting factors. However, even the intravenous administration of this compound is associated with a latent period of several hours. Therefore, in the immediate treatment of severe haemorrhage, *prompt administration of fresh whole blood is necessary*. Menadione (synthetic Vitamin K, Vitamin K₃) is ineffective in countering the bleeding caused by oral anticoagulants.

Rarely, coumarins may cause urticaria, anorexia, vomiting and diarrhoea. *Coumarin anticoagulants cross the placenta and may cause fatal hemorrhage in the fetus; further they have a teratogenic effect.*

WARFARIN SODIUM: This compound, originally employed as a rodent poison, is the most widely used coumarin anticoagulant and many consider it to be the drug of choice. After oral administration, absorption is essentially complete and the maximal plasma concentrations are reached in 2 to 12 hours. After an initial dose of 40-50 mg., a therapeutic prothrombin time is usually achieved in 36 hours and the effect lasts for a further period of 36 hours. Approximately 97 per cent of the drug is bound to plasma albumin. Unlike with bishydroxycoumarin, the plasma levels of warfarin are more steady during therapy.

If warfarin is employed for long-term anticoagulant therapy, it takes about 3 days for the prothrombin time to return to normal after drug discontinuation. Warfarin has the unique prop-

Table 29.2 : Dosage schedule for commonly employed oral anticoagulants

Drug	Dosage mg./day			Interval to max effect (Hours)	Remarks
	First	Second	Maintenance*		
Warfarin Sodium	10-15	10-15	2-15	36-72	See text
Acenocoumarin (Sintrom)	15-20	8-15	2-10	24-36	Oral ulceration and G. I. disturbances.
Phenylpropylhydroxycoumarin (Marcoumar)	30	10	1-5	36-72	Slow onset 2-3 days, cumulative, slow recovery.
Anisindione	200-300	100-200	25-150	24-72	

* Aimed at keeping the prothrombin time at 32-40 seconds, with a control of about 16 seconds.

erty of being water soluble, among the 'anti-prothrombin' drugs and if vomiting prevents oral administration, it can be administered by intramuscular, intravenous or rectal route.

Comparatively few toxic effects other than haemorrhage have been reported with warfarin. These include alopecia, urticaria and severe dermatitis. The drug probably has a mild bronchodilator activity and has been shown to dilate the coronary vessels in swine.

Warfarin sodium is available as 5 mg. tablets and is used once a day. The drug has a cumulative action and the maintenance dose may have to be gradually decreased after the first week or so. Unlike in the past, no loading dose is used to initiate therapy; maintenance doses are used from the beginning.

It is the only 'oral anticoagulant' available for parenteral administration. Warfarin sodium injection contains 50 mg. of the sterile drug powder in a vial. The dosage is similar to that employed for the oral route.

The important features of other bis-hydroxycoumarin derivatives are summarized in Table 29.2.

INDANDIONE DERIVATIVES: These include the compounds *phenindione*, *diphenindione*, *anisindione* and *chlorphenindione*. The compound used initially was phenindione and the others differ from it in the duration of action and incidence of toxic effects. The anticoagulant activity of these compounds is essentially similar to the coumarin compounds. Phenindione (Dindevan) has rapid onset and short duration of action. With the initial therapeutic dose, significant action is seen within 24 hours and therapeutic effect can be achieved within two days with maintenance dose. When treatment is stopped the prothrombin time returns to normal within 48-72 hours.

Adverse reactions include skin rash, fever, diarrhoea, agranulocytosis, extensive oedema, renal damage and jaundice. Some of these compounds turn the urine red-orange. Allergic reac-

tions, sometimes fatal, are more common than with coumarin derivatives.

Factors affecting the dosage and activity of the oral anticoagulants: Besides the fundamental genetic differences in rates of drug metabolism, factors like age, sex, body content of vitamin K and presence of liver damage can modify the intensity and duration of the anticoagulant effect. Further, the intake of other 'interacting drugs' can influence the variability in response. Thus,

(a) Poor diet, bowel disease and obstruction to the flow of bile into the intestine all cause vitamin K deficiency and enhance the response to oral anticoagulants. Oral antimicrobial drugs (except perhaps third generation cephalosporins) have little effect on anticoagulant therapy, except in situations mentioned earlier in this paragraph.

(b) Chronic alcoholism, liver disease, kidney disease and vitamin C deficiency all enhance the activity of oral anticoagulants.

(c) The butazolidines, large doses of aspirin, clofibrate, disulfiram, thyroxine, anabolic steroids, metronidazole, cotrimoxazole, chloral hydrate, and cimetidine can significantly prolong or intensify the action of oral anticoagulants and may produce severe haemorrhage in patients on oral anticoagulant therapy.

(d) Barbiturates, chloral hydrate, meprobamate, griseofulvin and haloperidol stimulate the microsomal enzyme system concerned with the detoxification of the oral anticoagulants and this may lead to a reduction in the anticoagulant effect. When these drugs are stopped, haemorrhages may occur due to excessive anticoagulant activity. It is safer to use diazepam as a hypnotic as it does not stimulate the liver microsomal enzymes. Alcohol is also known to interfere with anticoagulant effect.

(e) Drugs like tolbutamide and phenytoin may get accumulated in the body following coumarins and hence, doses of these drugs must be reduced.

The most important consideration in choosing an oral anticoagulant is probably the previous

experience of a clinician with the use of a particular drug. This is one field where individualization of therapy is most important.

EVALUATION OF ANTICOAGULANT THERAPY

In spite of extensive work, considerable confusion still exists about the value of anticoagulants in therapeutics. To understand the usefulness and limitations of anticoagulant therapy it is essential to realize the difference between a 'thrombus' (White thrombus) and a 'clot' (Red thrombus). Intravascular coagulation process may begin with the selective deposition of blood platelets and white cells, the mass being strengthened by coarse peripheral fibrin strands. In the case of an artery, because of the rapid blood flow, this mass does not have red cells, is pale, friable and non-homogenous. This, then, is a 'thrombus' (White thrombus). Platelet aggregation may be a more important event in the initiation of arterial thrombus. In contrast to this, a typical 'clot' (Red thrombus) results from the solidification of blood in the test tube. It is soft, dark red, and homogenous, and is made up of red cells, platelets, white cells and fibrin. The slow blood flow in a vein encourages the formation of 'clot' which has a much smaller platelet-leucocyte element and a considerable clot-like tail. In venous 'thrombosis' and pulmonary embolism the structure responsible for the clinical state is usually a clot, and not a 'thrombus' as occurs in artery. The drugs which interfere with the clotting mechanism may not necessarily modify the arterial 'thrombus' formation unless they affect the platelet behaviour. In other words, although such drugs may satisfy the conventional definition of an 'anticoagulant' they are not 'antithrombotic' agents. Arterial and venous thrombosis differ in their causes, their physiological effects and in their management.

Conventional anticoagulant therapy can prevent the extension of an existing venous thrombus and the development of additional thrombi in the vascular bed. *It does not influence the estab-*

lished thrombus, nor can it reverse ischemic tissue damage.

The exact role of clotting process in the mechanism of thrombosis is ill-understood. Thus, patients with very prolonged clotting time (e.g. after heparin) have fairly normal haemostasis, while persons with only a slightly increased clotting time (haemophilia) may develop severe haemorrhage on minor bruising. Ideally, therefore, the merits of anticoagulant drugs should be evaluated by their effect on thrombus formation, rather than by their action on the coagulation process. However, as all the criteria employed for control of anticoagulant therapy involve the measurement of their effect on the coagulation process, the use of anticoagulants is essentially empirical.

Heparin is the drug of choice when rapid induction of anticoagulation is desirable. It can be used safely in the mother during late pregnancy. The disadvantages of heparin are its high cost, the need for parenteral administration, and the frequency of local reactions at the site of injection. The oral anticoagulants have the distinct disadvantages of delayed onset of action, variable therapeutic effect and need for an elaborate and expensive laboratory control.

Combined therapy gives the patients the advantage of immediate and prolonged clotting effect with minimal discomfort and maximum economy.

The maximum therapeutic response to oral anticoagulants is achieved after 4-7 days after the initial dose. Hence, in order to obtain immediate therapeutic response, both heparin and an oral anticoagulant can be initially combined. For this purpose injection of heparin, given intravenously, intermittently at 4-8 hours interval, is usually recommended.

The indications for anticoagulant therapy are:

(a) **Venous thrombosis and pulmonary embolism:** Anticoagulants are most useful in the prevention and treatment of venous thrombosis and pulmonary embolism.

Fixed dose heparin considerably reduces the

incidence of pulmonary embolism, if used *prophylactically* in post-operative and postpartum therapy. For this purpose, heparin is given subcutaneously in subanticoagulant doses of 5000 units every 8-12 hours. Laboratory monitoring is not necessary. A highly concentrated solution of heparin should be used and should be injected subcutaneously, followed by pressure over the injection site to minimize local bleeding into the tissues. The risk of haemorrhage following low doses is minimal.

Such prophylactic use of heparin in low doses is also justified for prevention of deep vein thrombosis particularly in patients such as those confined to prolonged bed rest for some reason.

Anticoagulants are used in full doses prior to control of atrial fibrillation with quinidine, in order to reduce the risk of thromboembolism.

In the *treatment* of pulmonary embolism, heparin should be given promptly (20000-30000 units in 24 hours) and continued for one week or longer. Oral anticoagulants should be started 48 hours before stopping heparin and should be continued for several weeks later. A patient with single massive embolism following surgery or bed rest should receive anticoagulants for 3-6 months.

(b) **Myocardial infarction:** In patients with acute cardiac infarction, anticoagulants reduce thromboembolic complications and thus, may reduce the morbidity and mortality in patients put to a prolonged period of bed rest. These agents, however, do not seem to alter the chances of survival of a patient with cardiac infarction nor do they appear to prevent further recurrent fatal infarction in such cases. The long term prophylactic use of anticoagulants in persons with previous history of myocardial infarction confers a small initial benefit (1-2 years) on men under 55; the present evidence indicates that such therapy does not benefit men over 55 years or women.

The role of anticoagulant therapy in the management of 'angina pectoris' and of 'coronary insufficiency' is still not established.

It is difficult, therefore, to justify the routine

application of anticoagulants in all cases of myocardial infarction although it is true that occasionally a relatively mild case may develop sudden fatal thromboembolism, causing death. In general they offer very limited benefit as compared to the risk involved in such therapy.

(c) **Rheumatic heart disease:** The occurrence of emboli associated with rheumatic heart disease is an indication for long term anticoagulant treatment. Anticoagulants are used to prevent pulmonary arterial thrombosis in patients with mitral stenosis and pulmonary hypertension who are awaiting surgery.

(d) **Cerebrovascular disease:** Anticoagulants, as a rule, are not indicated in cerebrovascular disease for fear of causing cerebral haemorrhage. Their therapeutic usefulness is doubtful, except perhaps in the intermittent insufficiency syndromes, and stroke due to emboli from the heart.

(e) **Disseminated intravascular coagulation (DIC):** This is a condition which arises from many causes such as bacterial toxins, leakage of amniotic fluid into the maternal circulation and snake bite. The normal clotting factors are rapidly consumed leading to a hemorrhagic state. Paradoxically, heparin has been found to reverse the clotting defect and arrest the bleeding in some cases but in a few patients it may aggravate the bleeding.

(f) Anticoagulant therapy is of value in the treatment of sudden embolic occlusion of peripheral arteries, and in the treatment of frostbite and acute gangrene. The efficacy of these agents in the treatment of chronic peripheral vascular diseases is doubtful.

(g) They are also used in case of artificial heart valves in order to prevent emboli. For this purpose, heparin therapy is not enough; therapy with oral anticoagulants is required.

Contraindications to anticoagulant therapy:

(a) Haemorrhagic tendency and blood dyscrasias.

(b) Benign or malignant ulcers, such as in the

gut, colitis, diverticulitis, recent operation upon the CNS, eye or prostate gland.

(c) In subacute bacterial endocarditis, anticoagulants may cause detachment of the bacterial vegetations from the damaged valves into general circulation.

(d) Threatened abortion, injury to the brain and the spinal cord.

(e) Regional and lumbar block anaesthesia.

(f) Prothrombin deficiency, severe hepatic, renal impairment and malignant hypertension.

(g) An uncooperative patient, inadequate laboratory control and uninformed or casual medical supervision.

Requirements of an ideal anticoagulant:

(a) The therapeutic dose should produce a predictable and uniform effect on the coagulation mechanism which can be measured by a simple, rapid and inexpensive test.

(b) It should be effective orally and parenterally, and should not be toxic on repeated administration.

(c) It should have a rapid onset and a sufficiently prolonged duration of action and should not cause drug interactions.

(d) The anticoagulant effect should cease promptly following the discontinuation of the drug. It should be cheap.

No single anticoagulant which fulfils all of these conditions is available at present.

Agents used to prevent blood coagulation *in vitro*:

(a) Clotting can be delayed by cooling the blood or by collecting it in coated vessels so that platelets are not broken up. The coating used is paraffin, collodion or silicone.

(b) **Oxalates and citrates:** These act by removal of calcium ions. 0.1 per cent potassium oxalate precipitates serum calcium as calcium oxalate.

Sodium citrate combines with calcium and forms calcium sodium citrate. The anticoagulant solution B.P. contains 2.5 per cent of sodium

citrate in 0.9 per cent saline. Citrate is usually employed as an anticoagulant for blood to be transfused. The ultimate strength of citrate is 0.38 per cent. Potassium oxalate produces convulsions and hence is not employed *in vivo*.

(c) **E.D.T.A.** (Ethylenediamine tetraacetic acid) a chelating agent, has a great affinity for calcium and its sodium salt has been used as an anticoagulant.

(d) **Hirudin:** An extract obtained from leeches can act as an anticoagulant because of its high antithrombin activity. The preparation is likely to be toxic unless highly purified and is expensive.

(e) **Heparin:** discussed previously.

THROMBOLYTIC AGENTS

The process of fibrinolysis or dissolution of blood clot is schematically represented in Fig. 29.3.

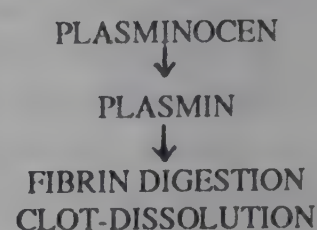


Fig. 29.3: Mechanism of fibrinolysis.

Normally, the euglobulin fraction of the plasma contains the inactive precursor plasminogen. Plasminogen, in the presence of certain enzymes, is converted to plasmin by an activator substance present in tissues and blood. The active proteolytic enzyme plasmin is capable of breaking down fibrin clots *in vitro*.

All thrombolytic agents currently in use act directly or indirectly as plasminogen activators. Plasminogen is the inactive proteolytic enzyme of plasma and binds to fibrin during the formation of a thrombus. This binding endows specific fibrinolytic properties on the plasminogen-plasmin enzyme system, since fibrin-bound plasminogen is more susceptible to the activation than is plasma plasminogen. The presently used

plasminogen activators are :

1. Streptokinase
2. Recombinant tissue-type plasminogen activator (rt-PA)
3. Urokinase
4. Acylated plasminogen-streptokinase activator (APSAC) complex and
5. Recombinant single chain urokinase plasminogen activator.

Of these, the first three agents are commercially available for therapeutic use and are discussed below.

Various agents differ in their propensity to activate plasma plasminogen; the rt-PA and probably single-chain urokinase plasminogen activator are termed "fibrin selective" because of their high ratio of activity for fibrin bound plasminogen as compared with plasma plasminogen. With the pharmacologic doses used in the treatment of acute myocardial infarction, the lytic activity is greatest with streptokinase, intermediate level with urokinase and least with rt-PA. Given I.V., the plasma half-life of these agents differ: rt-PA have a rapid turnover rate in blood, while streptokinase and urokinase have intermediate ratio. Thus, differences in pharmacokinetics and patient's tolerance and disease state dictate the duration of administration necessary to achieve an appropriate thrombolytic effect.

Therapeutically, when treatment is begun within the first 3 hours of the onset of chest pain in MI, a similar incidence of reperfusion is provided by all the agents, but there are considerable differences in the ease with which they can be administered. Re-thrombosis, after re-perfusion, occurs in roughly inverse proportion to the length of the plasma half life of the drug used, with the lowest incidence with urokinase and streptokinase, and the highest with rt-PA. Hence, heparin is administered simultaneously with rt-PA, primarily to enhance re-perfusion and decrease the rate of re-thrombosis. Since streptokinase and urokinase produce more prolonged and extensive coagulation defect, simultaneous ad-

ministration of heparin is not required.

Adverse effects : Bleeding is the commonest adverse effect with all these agents. Thrombolytic therapy induces a marked hemostatic defect by means of combined actions on blood components, the vessel wall and the hemostatic plug. It is probably much less with selective agents such as rt-PA. Streptokinase, being a bacterial protein, is antigenic. Hence, therapy with streptokinase is associated with an occasional allergic response and rarely (0.1%) anaphylactoid reaction; therapy with urokinase does not provoke allergic reaction. Hypotension occurs more often with rapid administration of streptokinase than with other agents. The optimal dose that would produce the highest rate of reperfusion and the lowest incidence of bleeding complications and rethrombosis is difficult to decide precisely. Because thrombolytic agents do not distinguish between the fibrin of a thrombus and the fibrin of a hemostatic plug, they are double edged weapons. From the experience with heparin, it appears that a hypocoagulable state is itself well tolerated and an unlikely initiator of bleeding in patients with an intact vascular system and in the absence of such risk factors as recent surgery, DU, thrombocytopenia or administration of other antithrombotic medication. Vascular injury, rather than changes in blood coagulation is the main cause of bleeding. The most important contraindications are factors indicating a predisposition to intracranial hemorrhage : untreated hypertension, recent cranial trauma, intracranial tumor, and history of cerebrovascular accident. In case of bleeding, the drug is stopped immediately; severe cases may be treated with antifibrinolytic agents such as epsilon amino caproic acid (EACA).

Probably 10-20% of reperfused arteries undergo rethrombosis. The ideal antithrombotic regimen to sustain successful reperfusion has not been definitively established; but heparin in standard doses (500 U) and aspirin (150 mg/day) have been routinely recommended. At present, the most popular approach to preventing re-

thrombosis in arteries is a combination of anticoagulation and angioplasty. Rethrombosis of veins is probably most often related to incomplete lysis of the original thrombus, and the present management emphasizes adequate anticoagulation with heparin as the best approach to preventing rethrombosis.

Therapeutic uses: It is now accepted that the addition of a fibrinolytic agent to an antithrombotic regimen accelerates the rate of vascular reperfusion. Furthermore, many associated physiologic and laboratory manifestations of vessel occlusion improve more rapidly than can be accomplished without fibrinolytic therapy.

(1) *Pulmonary embolism* : Unless contraindicated by serious haemorrhage, thrombolytic therapy has been recommended as the primary form of treatment for patient with massive pulmonary embolism. In less severe cases, more assurance of safety against bleeding complications would be required to justify such treatment.

(2) *Deep vein thrombosis* : Thrombolytic therapy used in early stages appears to be better than anticoagulant (heparin) therapy. However, lysis of 90% or more clot usually require several days of therapy. The present evidence indicates that heparin is not effective for the preservation of longterm venous valvular function, and that although thrombolytic treatment does not ensure long-term benefits, the post-phlebitic syndrome is often avoided by rapid, early and complete vascular reperfusion.

(3) *Peripheral arterial occlusion* : It is particularly used for dissolving occlusions of small arteries that cannot be surgically treated. Further, it may serve as a prelude to vascular surgery. Thrombolytic therapy for arterial thrombi in locations other than the limbs or the coronary arteries has been reported for virtually all organs. For this, the drug may be administered systemically or by regional infusions. A recent, cerebrovascular accident remains a contraindication to such therapy. Additional contraindications are other risk factors for intracranial haemorrhage, recent (within 10 days) major

surgery, active internal (GI) bleeding, and a pre-existing haemorrhagic tendency.

(4) *Myocardial infarction (MI)* : It is now well accepted that thrombolytic therapy, begun soon after an acute MI, reduces mortality and preserves left ventricular function. Among various thrombolytic agents available, streptokinase and recombinant tissue plasminogen activator (rt-PA) are commonly used at present. Although, such therapy is useful, even when used within the first hour after MI it rarely prevents the subsequent ECG and enzymatic changes indicating infarction. Streptokinase is given I.V. in the dose of 1.5 million units over 60 min. and rt-PA is given I.V. in the dose of 100 mg over 3 hours. This may be combined with aspirin 150 mg daily. There appears to be little difference in left ventricular function or predischage patency rates whether streptokinase or rt-PA is used. Both these drugs reduce early mortality, probably by a marked reduction in the size of the infarct. Streptokinase sometimes aggravates hypotension and this should be watched for.

These drugs are less useful 6 hours after infarction, and patients are not routinely treated other than with aspirin six hours after infarction unless they are at high risk.

All the plasminogen activators are effective thrombolytic agents when given in correct dosage for proper duration, at an appropriate time.

The biochemical properties of all agents dictate the treatment regimen. The longer the half-life of an agent, the longer the thrombolytic activity is maintained in the circulation. Consequently, streptokinase and urokinase can be administered by bolus injection, or short infusion without simultaneous administration of heparin, which can be given later, when recovery from the plasma coagulation defect begins. In contrast, rt-PA must be infused for 3 or more hours with heparin, in order to provide a continuous supply of fresh agent to the thrombus while preventing rethrombosis.

None of the agents, however, can be considered as ideal thrombolytic agents.

STREPTOKINASE: See Chapter 69.

UROKINASE: This enzyme, originally isolated from human urine, is now obtained from cultured human renal cells. It is a potent direct plasminogen activator. Unlike streptokinase, it is non-antigenic, non-pyrogenic and does not cause allergic reactions; further, it is a direct activator of plasminogen. The enzyme can induce predictable degree of fibrinolysis production and can lyse artificially produced clots in human veins. Urokinase appears to be the current treatment of choice in massive, acute pulmonary embolism. It is usually administered intravenously in an initial dose of 4400 units per kg. in 10 min. followed by continuous infusion of the same dose per hour for 24 hours. Its use is followed by administration of heparin and still later by oral anticoagulants. It is also used to lyse fibrin or blood deposits in the anterior chamber of the eye. For this purpose, 5000 units of the enzyme in 2 ml of sterile physiological saline at pH 7.2 to 7.6 are usually instilled into the anterior chamber.

Urokinase is contraindicated in conditions of hypofibrinogenemia and hypocoagulability of blood.

Tissue-type plasminogen activator (rt-PA) is a natural protein in man. It preferentially activates plasminogen bound to fibrin clot and thus avoids systemic activation of plasminogen; fibrinogen depletion and bleeding are thus minimized. It has recently been prepared by recombinant DNA technology. It is as effective as streptokinase but may be safer. It has a short half life of approximately 8 min. in circulating plasma. It is metabolised by the liver. It is given in the dose of 100 mg. i.v. initially in small amount as bolus followed by a slow infusion over a period of 2-3 hours. Heparin 5000 u is given i.v. bolus prior to administration of rt-PA.

ARVIN (Ancord): Arvin is a purified enzyme obtained from the venom of the Malayan Pit Viper, *Agkistrodon rhodostoma*. The enzyme removes fibrinogen from the blood by convert-

ing it to an imperfect fibrin polymer that breaks up easily in the circulation and is lysed. The enzyme thus produces fibrinogen depletion independently of the coagulation and fibrinolytic enzyme systems. Platelets are not affected. The therapy is controlled by measuring plasma fibrinogen.

The enzyme has been used with encouraging results in the treatment of venous thrombosis. It is administered intravenously in the dose of 2-3 units per kg. over a period of 6-8 hours, followed by slow intravenous injection of 2 units/kg every 12 hours. It promptly reduces the fibrinogen levels, the peak anticoagulant activity occurring 8 to 12 hours after its administration. The lowered fibrinogen levels return to normal within 3 weeks after cessation of therapy. It can also be used intramuscularly.

The major advantage of the enzyme appears to be that unlike the conventional anticoagulants, it does not cause a haemorrhagic tendency. However, bleeding may occur from a silent peptic ulcer or a surgical wound. Haemolytic anaemia, urticaria and unilateral impairment of vision have been reported. Specific antivenom antidote is available to treat the toxicity. Resistance to the enzyme may occur, particularly on intramuscular administration, due to antibody formation. There is little evidence at present about its ability to lyse an arterial thrombus.

AGENTS USED TO CONTROL BLEEDING

Bleeding can be controlled by physical methods such as application of pressure, tourniquet, cold and use of cautery. Drugs like pitressin and adrenaline can be used to produce vasoconstriction. Thus, pitressin (20 units) is used by infusion to reduce the portal venous pressure, thereby reducing the bleeding from oesophageal varices in cases of cirrhosis of liver. Adrenaline is used in the form of nasal pack to control epistaxis.

The use of coagulants in therapeutics is disappointing because it is difficult to have a drug which would produce coagulation at a specific

site without producing the systemic effect.

The coagulants can be divided into:

I. Agents acting locally: These agents control oozing of blood from minute vessels and are not effective in controlling bleeding from large vessels.

(a) **THROMBIN:** Thrombin is obtained from bovine plasma. It is stable as a dry powder stored between 2 to 8°C. It is, however, inactive below pH 5. Thrombin therapy is restricted to local application in oozing of blood. Thrombin has also been used, mixed with plasma, to anchor the skin grafts in place.

(b) **THROMBOPLASTIN:** Thromboplastin is a powder prepared from the acetone extracted brain and/or lung tissue of freshly killed rabbits. It is used for determination of prothrombin time and as a local haemostatic in surgery.

(c) **FIBRIN:** Fibrin obtained from human plasma is used in the dehydrated form as sheets from which segments of any desired size may be cut for use on bleeding surfaces. When used in combination with a thrombin solution, it also acts as a mechanical barrier and holds thrombin in position over the bleeding area.

(d) **GEL FOAM:** Gel foam is a porous, pressed form of gelatin sponge used in conjunction with thrombin to control oozing of blood from surface wounds. Gel foam is usually moistened with sterile, isotonic saline before use. It is completely absorbed within 4 to 6 weeks and hence, may be left in place after suturing of an operative wound. Gel foam is available as cones, packs, sponges and powder.

(e) **OXIDIZED CELLULOSE (Oxycel):** Oxycel is surgical gauze treated with nitrogen dioxide, and it promotes clotting by a reaction between hemoglobin and cellulosic acid. Oxycel, when wet with tissue juice, becomes sticky and gummy and exerts its haemostatic effect by mechanical blockage, which stimulates an artificial clot over the surface of the wound. Oxycel is usually absorbed completely within 2 to 10 days. It interferes with bone regeneration.

II. Agents acting systemically:

(a) **FIBRINOGEN:** Fibrinogen, a sterile fraction from human plasma, is used for restoring normal fibrinogen levels in haemorrhagic complications caused by acute afibrinogenemia. Fibrinogen and thrombin may be employed together for local haemostasis.

(b) **ANTIHAEMOPHILIC GLOBULIN (AHG):** Haemophilia A and Christmas disease (haemophilia B) are the two most common hereditary haemorrhagic states, due to deficiency of specific clotting factors VIII and IX respectively. Antihaemophilic globulin or concentrate of factor VIII (AHG) is highly effective in the treatment of classical haemophilia-A. High potency human AHG is prepared from pooled, normal, human plasma. It is standardized by its ability to shorten the clotting time of haemophilic blood. It is given intravenously, in the dose of 15-60 units/kg. daily. Simultaneous use of fibrinolytic inhibitors like EACA can reduce the dose required of AHG to achieve the results. In case of non-availability of AHG, fresh plasma or blood transfusion is used. The half-life of factor VIII in the blood of haemophiliac, is about 12 hours.

In patients with Christmas disease fresh or stored plasma infusion is indicated to replenish the factor IX.

(c) **PLASMA or BLOOD:** Fresh frozen plasma is suitable for the treatment of most coagulation disorders, since it contains all the clotting factors. Concentrate of factor VIII (purified) and a partially purified preparation containing factors II, VII, IX and X are also available for specific deficiencies. Whole blood for replacement of coagulation factors may not be ideal as large volumes are required and it carries the risk of transfusion reactions; it is, however, useful when R.B.C. transfusion is also necessary.

(d) **CALCIUM:** Calcium therapy, particularly by parenteral route, is often resorted to for control of bleeding. Except in the presence of calcium deficiency such treatment is not useful.

(e) **VITAMIN C and RUTIN (Vitamin P):** Vitamin C can control bleeding only in the presence

of scurvy. Rutin, a glycoside widely prevalent in plants, has been employed clinically in the treatment of increased capillary erythropermeability. Rutin is less effective if there is an accompanying vitamin C deficiency, so that both these agents are usually administered together. The oral dose is 20 to 30 mg. of rutin with 50 to 100 mg. of vitamin C, repeated 3 to 4 times a day.

(f) **CERTAIN SNAKE VENOMS** especially Russel Viper and copper Head snake venoms, enhance coagulation by stimulating thrombokinase.

(g) **VITAMIN K:** Vitamin K, a fat soluble vitamin, is not a single entity but occurs naturally in the form of at least two distinct substances, vitamin K₁ and vitamin K₂. Both are derivatives of naphthoquinone.

Vitamin K₃ or menadione is a lipid-soluble, synthetic, naphthoquinone compound which is as active as vitamin K on molar basis.

Vitamin K occurs as a bright yellow crystalline powder while menadione is a light yellow oil. The sodium bisulfite salt and the tetrasodium salt of the diphosphoric acid ester of menadione are soluble in water.

Pharmacological actions: Vitamin K is essential for the biosynthesis of prothrombin and factors VII, IX and X. It participates in the carboxylation of the glutamic acid residues of these proteins in the final stage of their synthesis. Vitamin K is also shown to be involved in electron transport (coenzyme) and oxidative phosphorylation.

Apart from the action on blood coagulation, vitamin K and menadione do not possess any other pharmacological actions.

Absorption, fate and excretion: Vitamin K is produced by the flora of the human intestine. The fat soluble vitamin K₁ and K₂ are absorbed in the presence of bile salts, while the water soluble menadione salts are absorbed even in their absence. The exact daily requirement of vitamin K is not known. Both the lipid and water soluble preparations are satisfactorily absorbed on parenteral administration. The metabolic fate of vita-

min K is not known.

Adverse reactions: Adverse reactions are rare after oral administration. However, serious reactions, including fatalities, have occurred following intravenous use. These reactions resemble anaphylaxis. Large doses of synthetic menadione have produced haemolytic anaemia, hyperbilirubinemia and kernicterus in newborn, especially in premature infants. Menadione competes with bile salts for glucuronide detoxification mechanism causing the accumulation of bile salts in the blood and this results in jaundice. Haemolysis with menadione is usually seen in infants, whose erythrocytes lack the enzyme glucose-6-phosphate dehydrogenase. Patients with liver disease should not be given repeated, large doses of vitamin K, if the response to the initial dose is unsatisfactory.

Therapeutic uses: The indication for administration of vitamin K is hypoprothrombinemia, which may be due to:

(a) Hepatocellular disease e.g. toxic or infectious hepatitis and liver cirrhosis.

(b) Obstructive jaundice.

(c) Chronic diarrhoea, extensive bowel resection, prolonged oral antibiotic therapy.

(d) As the newborns lack the normal intestinal flora, they may suffer from a relative vitamin K deficiency and hypoprothrombinemia. Routine prophylactic administration of vitamin K₁ 0.5 to 1 mg. to newborn infants after delivery is recommended by some authorities.

(e) Following oral anticoagulant and salicylate therapy: For the treatment of oral anticoagulant toxicity, vitamin K₁ oxide is superior to menadione. It is administered intravenously in the dose of 50 to 100 mg. The rate of administration should not exceed 5 mg. per minute, otherwise cyanosis, flushing and peripheral collapse may develop.

Preparations:

(a) Vitamin K₁ (Phytomenadione) tablet 10 mg., ampoules 10 mg. per ml. of vitamin K₁ oxide.

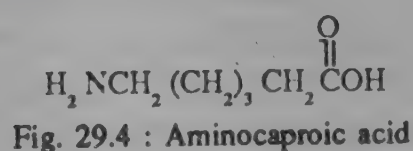
(b) Menadione tablet 5 mg. and 10 mg. am-

poules 3 to 10 mg. per ml.

(c) Menadione sodium bisulfite injection I.P.: by subcutaneous, intramuscular or intravenous route 1 to 2 mg. daily. In emergencies, 10 to 50 mg. intravenously every 4 hours according to prothrombin activity of the blood.

(d) Menadione sodium diphosphate (Synkavite) tablet 5 mg., ampoules 10 mg./ml. and 100 mg. in 2 ml.

EPSILON AMINOCAPROIC ACID: (E.A.C.A.): Epsilon aminocaproic acid is a white, crystalline substance soluble in water and structurally related to lysine. It can be administered by mouth or by parenteral route. It blocks the plasminogen activation by competitive blockade and thus reduces fibrinolytic activity (Fig. 29.4). Given orally it is rapidly absorbed and the peak level after a single dose is achieved in about 2 hours. The drug is mainly excreted by the kidney, largely unchanged, 60 to 90 per cent of the total administered dose appearing in the urine within 24 hours. A blood level of 13 mg. per 100 ml. is required for plasminogen inhibition, whereas 130 mg. per 100 ml. inhibits plasmin activity.



Adverse reactions: The drug has been reported to produce minor side effects such as nasal stuffiness, abdominal discomfort, dyspepsia, hypotension, conjunctival erythema, nausea, vomiting, diarrhoea and skin rash. A lethal complication is disseminated intravascular thrombosis.

Preparation and dosage: Aminocaproic acid (Amicar): Initial dose-oral or slow intravenous, 5 g. followed by 1 g. every 1 hourly till satisfactory response is obtained.

Therapeutic uses: Continuous uncontrolled haemorrhage associated with excessive fibrinolytic activity, not responding to the usual th-

erapeutic modalities, has been considered an indication for E.A.C.A. therapy. Thus, the drug has been used to control haemorrhage in abruptio placentae, post-partum haemorrhage and haemorrhage following certain surgical procedures. It has been claimed that prophylactic administration of EACA (100 mg./kg I.V. or orally 4 times daily) can reduce measured blood loss after prostatectomy by about 50%. The drug has also been used similarly to reduce blood loss in normal children undergoing tonsillectomy.

It must be emphasized that aminocaproic acid is of no value in treating haemorrhage due to thrombocytopenia or most other coagulation defects. It should not be used in patients with disseminated intravascular clotting and in those who are thrombosis prone.

Other synthetic inhibitors of fibrinolysis include tranexamic acid (AMCA) and p-aminomethyl benzoic acid (PAMBA). Tranexamic acid is about 10 times more potent than EACA and it persists longer in the tissues. It is used in the dose of 1 g. orally or i.v., 3-4 times a day.

SCLEROSING AGENTS: Sclerosing agents are irritating substances employed to obliterate varicose veins. They have also been employed for closure of hernial rings and for fibrosing uncomplicated haemorrhoids.

The important preparations are:

(a) Sodium morrhuate injection: This is a sterile solution of the sodium salts of the fatty acids of cod liver oil. It is marketed as 5 per cent aqueous solution, containing 2 per cent benzyl or ethyl alcohol as a preservative. The dose is usually 0.5 ml. intravenously. Allergic reactions may develop occasionally.

(b) Other preparations containing salts of fatty acids include Sodium linoleate. The dose varies from 0.5 to 5 ml. by intravenous route.

(c) Ethanolamine oleate 5%. Dose: 2-5 ml. divided between 3-4 sites.

(d) Sodium tetradecyl sulfate is an anionic detergent, marketed as 3% solution: given I.V. as 0.5-1.0 ml at upto 4 sites.

30 Drugs Effective in Iron Deficiency Anemias

A decrease in the oxygen carrying capacity of the blood is termed 'anemia'. The oxygen carrying capacity is determined by the haemoglobin content of the erythrocytes. Hence, a reduction in the blood haemoglobin level and in the number of circulating erythrocytes are the characteristics of anemia.

Erythropoiesis: The erythrocytes are produced in the bone marrow and are destroyed by the reticuloendothelial system. The maturation of erythrocytes occurs through several stages. The precursor cell in the bone marrow is the proerythroblast or haemocytoblast, which is subsequently converted to early, intermediate and late normoblast. The nucleus of the late normoblast becomes pyknotic along with the appearance of a reticulum, resulting in the formation of a reticulocyte. It takes the reticulocyte approximately 4 days to mature into a normal erythrocyte. The normal life span of a human erythrocyte is roughly 110 to 120 days.

Various factors such as oxygen lack, vitamin C, growth hormone and thyroxine stimulate erythropoiesis. The kidney produces a glycoprotein termed erythropoietin which has an important regulatory action on erythropoiesis. Deficiency of various dietary factors such as iron,

folic acid and vitamin B₁₂ disturbs the normal erythropoiesis resulting in anemia.

Anemias may, thus, be classified according to their etiology.

I. Anemias due to dietary deficiency of factors essential for normal blood formation, e.g. iron, folic acid, vitamin B₁₂, vitamin C, and pyridoxine.

II. Anemias due to blood loss such as menorrhagia, G.I. loss and hookworm infestation.

III. Anemias due to excessive blood destruction, e.g. sickle cell anemia, autoimmune haemolytic anemia and porphyria.

IV. Anemias due to aplasia or hypoplasia of the bone marrow. Aplastic and hypoplastic anemia, such as idiopathic or following certain drugs.

V. Anemias of uncertain origin, e.g. due to infection, rheumatoid arthritis, liver disease and widespread malignant disease.

IRON METABOLISM

Iron deficiency anemia is caused by deficient synthesis of hemoglobin of which iron is an important constituent. Iron is present in every cell in the body. The total iron content of the body

Table 30.1 : Distribution of total body iron in adults

	Male 70 kg. Hb. 16 g./100 ml (g.)	Female 45 kg. Hb. 12g./100 ml. (g.)
Haemoglobin Fe	2.67	1.26
Storage Fe	0.5 - 1.5	0.5 - 1.5
Myoglobin Fe	0.122	0.077
Transport Fe	0.003	0.003
Cellular or parenchymal Fe	< 0.300	< 0.300

Ref: Carl, Moore: Iron Metabolism and Nutrition: The Harvey Lectures, Series 55: 67-101. 1959-60. By courtesy of the Author and the Publishers.

usually varies between 2 to 5 gm. depending upon the body weight and hemoglobin level. There is a difference between men and women. Thus, in adult males the iron content is estimated to be about 50 mg. per kg. body weight as compared to only 35 mg. per kg. body weight in adult females. The body iron is distributed mainly in two forms: (i) as heme, in hemoglobin, myoglobin and in cytochrome oxidase and other enzymes and (ii) iron bound to protein without heme formation, as storage compounds ferritin and hemosiderin, and as transport iron bound to transferrin.

Hemoglobin has an iron-containing moiety, metalloporphyrin or heme, combined with the protein globin. The molecular weight of hemoglobin is 64,500. Porphyrin consisting of 4 pyrrole rings and the protein globin are both synthesized in the body. About 2/3rds of the total body iron is in the form of hemoglobin.

Myoglobin is the heme protein of skeletal and cardiac muscle with molecular weight 16,800.

Parenchymal iron is the iron present in the cells as a component of various enzymes. There are many iron compounds in the body which are not related to erythropoiesis. Some are concerned with tissue respiration while a wide variety of metabolic processes in all cells involve enzymes which contain iron or require iron as a co-factor.

Iron absorption: Iron is normally ingested in the form of food. It must be emphasized that the amount of iron available from a given food depends upon its iron content as well as absorbability which differs with different foods. Iron from animal foods is generally better absorbed than that from vegetable foods. Heme iron is by far the most available and its absorption is independent of the composition of food. However, non-heme fraction represents by far the largest amount of dietary iron and hence it is important from the practical point of view. Green vegetables, peas and beans, bananas, spinach, some cereals, egg yolk, meat and liver are rich in iron.

The mean absorption of iron from vegetable foods ranges from 1% for rice, 5% for wheat to 6% for soyabeans, while for animal foods it

ranges from 11% for fish, 12% for hemoglobin to 13% for liver. Milk and milk products are a poor source of iron. Use of iron cooking utensils increases the iron content of food. Studies with radioactive iron in humans have demonstrated that absorption of inorganic iron salts can occur from any part of the gastrointestinal tract; however, there exists an absorption gradient, decreasing from the duodenum to colon. Thus, maximum iron absorption occurs in the duodenum.

A number of factors affect the absorption of iron. These are:

(a) In man, food iron must be reduced from ferric to ferrous form before it is absorbed. This reduction begins in the stomach and continues in the small intestine. Ionisation of food iron takes place in the stomach under the influence of gastric hydrochloric acid, pH lower than 5 being essential for adequate ionisation. Hypochlorhydria may thus reduce the amount of iron absorbed from the food. However, iron deficiency is not common in pernicious anemia, where achlorhydria is characteristic.

(b) Normally, only about 5 to 10 per cent of the total food iron is absorbed. Individuals with iron deficiency, however, absorb 20 to 30 per cent of the food iron. Thus, in subjects with severe iron deficiency, the absorption of iron in organic form (vegetables and meat) is approximately doubled, while the absorption of inorganic iron is increased 5 to 6 fold.

(c) Reducing agents present in the diet, such as ascorbate, succinate, and the SH groups of amino acids like cysteine, and proteins convert ferric iron to ferrous form and help the iron absorption.

(d) A diet poor in phosphorus enhances iron absorption, while phytates and organic phosphate compounds as in vegetarian foods form relatively insoluble and thus unabsorbable complexes with iron. Wheat is rich in phytates and consequently only about 5 per cent of wheat iron is absorbed, which increases to only about 7 per cent during iron deficiency. Egg iron is strongly complexed to the phosphate of yolk phosphoproteins and is poorly absorbed.

(e) Antacids such as calcium carbonate, aluminium hydroxide and magnesium hydroxide reduce iron absorption possibly by neutralizing the gastric acidity.

(f) Absorption of iron is reduced by its administration along with or after food. However, in therapy, ferrous salts are usually administered after food to minimize the irritation of the gastrointestinal tract.

(g) The pancreatic secretion has an inhibitory effect on iron absorption. In severe chronic pancreatitis and liver cirrhosis, iron absorption is greatly increased. The addition of pancreatin to the diet prevents this excessive absorption. Pyridoxine deficiency also enhances iron absorption despite elevated plasma iron levels.

(h) Lastly, partial gastrectomy and extensive bowel surgery reduce absorption of food iron. Absorption of inorganic iron salts, however, is less impaired. Cachexia, infectious diseases and malabsorption syndrome reduce iron absorption.

Mechanism of iron absorption: The iron is absorbed via the brush borders of the intestinal lining cells. Absorption of iron depends as much on its form as on its absolute amount. Two mechanisms for iron absorption have been postulated. These are:

(a) *An active transport process* with enzymatic or carrier characteristics which operates primarily at doses of iron that occur in a normal diet. This was explained by the mucosal block theory, initially described by Hahn and Granick in 1956. According to this theory, iron combines with the protein apoferritin in the villous epithelial cells to form ferritin. The absorption of iron is controlled by the availability of apoferritin. If this is fully saturated to ferritin, no more iron is absorbed. Thus, in normal individuals the body is protected from possible excessive absorption of the metal. It is claimed that the low serum iron and the anoxia due to anemia enhance the breakdown of ferritin and consequently make more apoferritin available, thereby augmenting iron absorption. The existence of such a mucosal block is supported by the observation that previ-

ous administration of a stable iron salt effectively reduces the absorption of a test dose of radioactive iron.

This control by the mucosal block, however, is relative and partial. Thus:

(i) The amount of iron in the food is too low to produce complete apoferritin saturation.

(ii) Hemoglobin iron is absorbed perhaps as intact heme and mucosal block does not operate for iron in organic form as present in food.

(iii) On oral administration of radioactive iron, as the size of the test dose increases, the total amount of iron absorbed also increases, although the percentage retained becomes less. Thus, the amount of total iron absorbed continues to increase even when the oral test dose reaches 300 mg.

(iv) Iron absorption is greater than normal not only in iron deficiency but also in conditions where plasma iron levels are high e.g. in anemia due to pyridoxine deficiency and hemochromatosis. Similarly, in dogs made acutely anemic by phlebotomy, iron absorption from gastrointestinal tract remains enhanced even when the anemia is corrected by total blood replacement. Hence the iron absorption is not so much influenced by plasma iron level or the degree of anemia and anoxia as by the tissue iron concentration and rate of erythropoiesis. It seems that iron deficiency, decreased iron stores and accelerated erythropoiesis due to any cause increase iron absorption.

It is now believed that the small quantity of iron as occurs in a normal diet is mostly absorbed by an active transport process probably involving its attachment to nonferritin protein. In iron repleted subjects, most of the iron fails to pass through the mucosal cells but becomes bound to apoferritin to form ferritin. This intracellular ferritin is eventually excreted following desquamation of the epithelial cells into the intestinal lumen, as a part of the regular shedding of the intestinal mucosa. In iron deficient subjects, however, the amount of apoferritin synthesized is reduced and iron passes through the cells into the plasma.

(b) A *passive transport process*, by which iron diffuses across the intestinal villi perhaps in combination with amino acids such as glycine and serine, has been recently described. This mechanism probably operates primarily at doses of iron exceeding those in a normal diet.

Iron transport and utilisation: After absorption, iron circulates in the blood bound to a beta globulin fraction, siderophilin or transferrin. Transferrin is present almost exclusively in the plasma and the extravascular space, and serves to transport iron from the site of absorption and storage to the areas of its utilisation. The liver parenchymal cells are the major site of transferrin synthesis.

Transferrin is normally one-third saturated with iron. Plasma iron is normally in equilibrium with iron stores. The normal plasma iron level varies between 66-146 $\mu\text{g.}/100\text{ ml.}$ The plasma iron level and plasma unsaturated binding capacity are modified by:

(a) Iron deficiency which is associated with a reduction in serum iron levels and an increase in iron binding capacity.

(b) Haemochromatosis which is associated with high serum iron levels and reduced binding capacity. A similar picture is seen in pernicious and aplastic anemias and

(c) Acute and chronic infections which are generally associated with reduced serum iron and decreased binding capacity.

The labile iron pool (mainly ferritin) is that part of body iron which is readily available for utilization for haemoglobin synthesis. Iron quickly enters this pool after absorption from the intestine, after release from the RBC breakdown and following parenteral injection. If the amount entering this labile pool is in excess of needs, then it is transferred into storage pool.

The daily iron turnover has been estimated to be approximately 35 mg. The major contribution to this, 21 mg., comes from the normal red cell destruction. About 3 million red cells are destroyed every second. Iron released from the destroyed red cells is thus reutilised. About 11

mg. of iron is contributed by that fraction which is not used for hemoglobin production during its stay in the marrow while the remaining 2-3 mg. comes from the storage sites, intestinal absorption and the extracellular fluid.

From these 35 mg. of iron, about 32 mg. enter the 'erythropoietic labile pool', a poorly defined compartment, primarily in the bone, for erythropoiesis. Approximately 1 mg. of iron goes for storage and into the extracellular fluid each and about 1 mg. is excreted, mainly in urine and sweat.

Iron transfer to maturing erythrocytes occurs mainly by release from transferrin to specific receptor sites on the membrane of the erythrocyte precursors. The insertion of iron into the porphyrin ring to form heme is now considered to be controlled by enzymes situated in the cell mitochondria. Failure of this process causes 'sideroachrestic anemias'. The anemias of lead poisoning and of thalassemia are of this type. In such cases iron granules are seen in the cytoplasm of erythroblasts.

Malignancy, infection, inflammation and uraemia diminish the utilization of iron administered orally or parenterally.

Iron storage: About 30 per cent of the total body iron is in the form of storage iron. This amount is vital, since iron deficiency anemia does not appear until the stores are largely depleted. Iron is stored predominantly in the form of ferritin and hemosiderin in bone marrow, liver, spleen and other areas with prominent reticuloendothelial components. The iron content of these compounds is 23 per cent and 35 per cent respectively, and it is present in the ferric form. Hemosiderin is probably a polymer of ferritin but unlike ferritin, it is not soluble in water. Conversion of iron to ferritin in the body is rapid. The normal stores vary from 0.5 to 1.5g. Both ferritin and hemosiderin are available for heme synthesis in the event of iron deficiency.

Iron stimulates ferritin synthesis. The concentration of ferritin is normally directly related to body iron stores. Serum ferritin measurement,

therefore, can be used to evaluate body iron stores. Usually 1 μg /l. of serum ferritin corresponds to 8 mg. of storage iron.

Iron excretion: Iron is tenaciously conserved. The body iron is regulated mostly by regulation of iron absorption by the gut. The total daily iron excretion is 0.5 to 1 mg. The channels of iron excretion are:

(a) Small excesses of iron are converted back to the ferric state within the villous epithelial cells where they combine with apoferritin to form ferritin. This is excreted in the faeces with the exfoliation of the villous cells. The life span of a villous cell is approximately 3 days. Iron is also lost by desquamation of the skin and hair.

(b) Small traces of iron are lost in bile and a small amount in sweat. However, in tropical climate like in India, sweat may be a major channel of iron excretion and amounts as high as 2 to 3 mg. may be excreted daily in sweat.

(c) Urinary iron excretion is 0.1 mg. daily but may be increased with proteinuria or iron overload.

(d) The additional iron loss due to menstrual bleeding in women, spread evenly over the 28 days of the cycle, is 0.3 to 0.6 mg. per day and upto 1.5 mg. appears in milk daily during lactation.

Iron requirements and sources: The daily diet in Western countries contains approximately 10-20 mg. of iron. Of this, normally 5-10 per cent is absorbed. The approximate daily dietary requirement of iron is 8-18 mg. for children, 15-20 mg. for menstruating women and 10-15 mg. for men. The fetus accumulates 200-400 mg. of iron, mainly in the last trimester; further, iron is lost during childbirth and later during lactation. Pregnant and lactating women, therefore, would need 20-25 mg. of iron daily in food. The monthly blood loss during menstruation is roughly 50 ml., equivalent to 25 mg. of elemental iron. Vegetable foods rich in iron include cereals like bajra, rice bran, whole wheat flour, pulses like Bengal gram, many leafy vegetables, condi-

ments like turmeric and tamarind pulp and jaggery. The iron content of milk is so poor (0.2 mg.%) that an infant fed on cow's milk alone would need 10 litres of milk daily to get its daily requirement of iron! Among the non-vegetarian foods, crab muscle, meat, liver and heart have a rich iron content.

Preparations and dosage:

I. For oral use:

(a) Dried or exsiccated ferrous sulfate I.P. is a greyish white powder, tablet 200 mg.

(b) Ferrous sulfate syrup. U.S.P. 60 mg. of ferrous sulfate (12 mg. of iron) in 5 millilitres.

(c) Ferrous sulfate paediatric drops for infants contain 125 mg. of ferrous sulfate (25 mg. of iron) in each millilitre. Ferrous sulfate is mixed with a reducing agent like glucose or ascorbic acid in the fluid preparations to prevent its oxidation.

(d) Ferrous gluconate I.P. is a yellowish-grey or pale greenish yellow powder or granules available as 300 mg. tablets. Elixir of ferrous gluconate contains 36 mg. of iron per 5 ml.

(e) Ferrous fumarate is a reddish brown salt relatively resistant to oxidation: 200 mg. tablets.

(f) Iron and ammonium citrate I.P. is a scaly ferric preparation soluble in water and is administered in the form of a mixture in the dose of 2 g. three times a day.

Various other iron preparations such as ferro-glycine sulfate, ferric choline citrate, ferrous calcium citrate, iron carbohydrate complex and iron chelates offer no remarkable advantage over the preparations described. In fact, the absorption of iron is lower from ferrous citrate, tartrate carbonate and pyrophosphate. Sustained release and enteric coated iron preparations are generally poorly dissolved in the gastric and intestinal secretions and may largely be lost in the stool.

II. Parenteral preparations:

(a) Iron dextran (Imferon) for intramuscular administration available as 5 ml. ampoules containing 50 mg. of elemental iron per ml. It can also be given intravenously as an infusion.

(b) Iron-sorbitol-citric acid complex (Jectofer) is a dark brown solution for intramuscular injection in 5 ml. ampoules containing 50 mg. of iron per ml.

(c) Iron-carbohydrate complex (Uniferon) contains iron, dextran, sorbitol and citric acid stabilized with gelatin. It is given intramuscularly. Each ml. contains 50 mg. of elemental iron.

Indications for iron therapy:

(I) *Prophylactic*, in pregnancy, infancy and childhood; in menstruating women, in professional blood donors and following gastrectomy.

(II) *Therapeutic*, in cases of iron deficiency anemia:

(a) Nutritional deficiency due to deficient intake or decreased absorption.

(b) Anemia of pregnancy and infancy.

(c) Anemia due to acute or chronic blood loss e.g. menorrhagia, peptic ulcer, piles, and hook-worm infestation. Hemoglobin contains 0.33% of iron. Hence, in a subject with 15 gm.% hemoglobin level, 100 ml. of blood loss equals a loss of 50 mg of iron.

As iron deficiency develops, iron stores diminish, as reflected by reduced and later absent stainable iron, hemosiderin. The most sensitive diagnostic test for detection of early or mild iron deficiency is the iron staining of the bone marrow. In fact, prelatent iron deficiency is characterized by the absence of stainable iron in the bone marrow, increased iron absorption but no decrease in either serum iron or hemoglobin concentration.

The iron deficiency anemia is characterised by

the presence of small erythrocytes (microcytosis) poorly filled with hemoglobin (hypochromia) and many cells of bizarre shapes (poikilocytosis) and variable sizes (anisocytosis). All hypochromic anemias, however, are not due to iron deficiency. There is now considerable evidence available that the metabolic importance of iron extends far beyond the red cell. Even in the absence of anemia, iron deficiency can produce adverse effects on brain function abnormalities in behaviour and mental performance in children improves after iron therapy.

The aims of treatment of iron deficiency anemia are: (a) correction of the hemoglobin and tissue iron deficiency and (b) recognition, and if possible, correction of the underlying cause.

Routinely, iron should always be administered orally.

Evidence to show that any one of the oral iron preparations is superior to others in raising the hemoglobin level or in reducing the adverse reactions is lacking. Since other preparations do not seem to have any obvious advantage over ferrous sulphate, which is the cheapest iron preparation, it is generally preferred. Tablets are more convenient than fluid preparations; further, they do not blacken the teeth and the tongue. The fluid preparations, however, are preferred in children and in the presence of dysphagia.

The great majority of patients do not experience any significant adverse effects with 200 mg. of dry ferrous sulfate three times daily after food. Absorption of ferrous sulfate in the usual therapeutic dose varies from 20 to 50 per cent in iron

Table 30.2 : Iron preparations available for oral therapy

Preparation	Total dose mg.	Total iron content mg.	Per cent utilisation of iron
1. Exsiccated ferrous sulfate	600	180	15
2. Ferrous gluconate	900	108	11
3. Ferrous fumarate	600	198	15
4. Iron and ammonium citrate	6000	1200	1.5 to 3

* 1 to 3 given either as tablets or in liquid form
4 given only in liquid form.

deficient patients. If it is not tolerated, the dose should be reduced or other preparations such as ferrous gluconate or ferrous fumarate may be tried.

During pregnancy, women should receive oral iron supplements prophylactically from the fourth month onwards and this should be continued during the lactation period.

Prophylactic iron therapy is also advocated for infants and children, more so in those with low birth weights. The average daily dose of ferrous sulfate in the form of syrup or pediatric drops varies from 100 to 200 mg.

Professional blood donors should receive routinely 300 mg. of ferrous sulfate daily for 1 month after each donation of 500 ml.

Following oral iron, normal hemoglobin level is usually attained within 1 to 3 months, depending mainly on the initial hemoglobin level. It is important, however, to continue with the therapy for 12-20 weeks after the hemoglobin level has returned to normal, in order to replenish the depleted iron stores.

The response of a patient with iron deficiency anemia to iron therapy is quite predictable. The reticulocyte count in the peripheral blood begins to rise within a week and reaches a peak at 10 to 14 days and returns to normal after about 3 weeks. Reticulocyte response is more striking in children than in adults; however, in children with hemoglobin more than 7.5 g. per cent and in adults, the rise in hemoglobin level may be the only indication of response to iron therapy.

The response to oral iron is considered satisfactory when the hemoglobin level increases by about 1 per cent (Sahli's method) per day, with rise of at least 10 per cent (1.5 g./100 ml. of blood) within three weeks. Most patients respond to oral therapy satisfactorily if iron is taken regularly and it is absorbed. Failure of a patient to respond to adequate oral iron therapy may be due to:

- (a) Incorrect diagnosis.
- (b) Uncooperative patient who does not take the medication regularly.

(c) Continued blood loss at a rate greater than that of regeneration.

(d) Superimposed infection, malignancy, inflammation or uraemia which reduce iron utilization.

(e) Defective absorption of iron from the gastrointestinal tract.

Adverse reactions to oral iron: All iron preparations are probably equally toxic per unit mass of soluble iron. They produce mild gastrointestinal disturbances characterised by colicky pain, nausea, vomiting, diarrhoea and gastric distress in about 6 to 12 per cent of individuals. These disturbances can be minimised by giving iron preparations after food and by a gradual increase in the dosage. The daily dose should not exceed six 200 mg. tablets of exsiccated ferrous sulfate. Iron administered in mixtures may combine with sulfide ions in the mouth forming black iron sulfide which causes blackening of teeth; this can be avoided by using a straw for drinking. Oral iron invariably makes the faeces black due to iron sulfide; this may interfere with detection of occult blood in the stools.

Acute iron poisoning is rare in adults but is not uncommon in children and infants. Doses of 1 g. or more of ferrous sulfate are considered toxic in children. Ingestion of large doses of iron is associated with severe gastrointestinal irritation resulting in hematemesis, vomiting, diarrhoea and shock as manifested by cyanosis, metabolic acidosis, cardiovascular collapse and coma. Death may occur within 12 to 48 hours. Even if recovery occurs, sequelae such as gastrointestinal obstruction may prove troublesome. *Every patient should be warned to keep the tablets away from children who may mistake them for sweets.*

Indications for parenteral iron therapy: It must be emphasized that response to therapy with oral or parenteral iron preparations is essentially similar, with average daily haemoglobin rise of about 0.2 g%. Hence, parenteral therapy is used only under special circumstances:

- (a) Failure to absorb adequate amounts of oral iron e.g. patients with malabsorption syndrome

or extensive bowel resection.

(b) Inability to tolerate oral iron and in patients with ulcerative colitis, colostomy or intestinal shunts.

(c) Exhausted iron stores in patients with chronic bleeding, in whom the average daily iron loss equals or exceeds the absorption of iron from oral ferrous sulfate.

(d) When the patient cannot be relied upon to take oral iron medication.

The dose is calculated on the basis that 25 mg. of elemental iron are needed to correct 1 per cent deficit of hemoglobin as measured by Sahli's method. To this dose is added half of the calculated amount for replenishing body iron stores.

Iron dextran and iron sorbitol citric acid complex are the two commonly used preparations. They are injected deep into the upper and outer quadrant of the buttock. The injection is made by 'Z' technique, pulling the skin and subcutaneous tissue to one side before entering the muscle to avoid leakage and skin staining. After an initial test dose of 25 mg., 100 mg. are given daily or every few days till the total calculated dose is administered. A single dose should not exceed 25 mg. for infants, 50 mg. for children and 100 mg. for adults.

Mobilization of iron dextran from intramuscular injection site varies from 50-90 per cent. Iron dextran, unlike iron sorbitol citric acid, does not saturate transferrin rapidly. It is absorbed from the muscle via the lymphatics and is converted by hepatic parenchymal cells into ferritin which in turn releases iron for hemoglobin synthesis.

Utilization of iron injected intravenously is 70 to 100 per cent. The initial dose of intravenous iron preparations is usually 20 to 30 mg. of iron (1-1.5 ml.). It is gradually increased to 100 to 200 mg. (5-10 ml.) and repeated daily, till the total dose is given.

Intravenous infusion of *total dose* of iron dextran in 5 per cent glucose or normal saline, given as a single injection has been reported; the drug concentration in the infusion must not ex-

ceed 5 per cent. The initial rate of the infusion is 10 drops per minute. If no ill effects are seen over 15 minutes, the rate may be increased to 40 drops. Although a satisfactory response is obtained, there is no evidence to indicate that the response is more rapid than that obtained by other conventional methods nor is it an alternative to blood transfusion. The incidence of severe adverse reactions varies from 1 to 6 per cent and hospitalization is essential. It is a potentially dangerous procedure and should be avoided if possible. The merit of this therapy is that the patient gets the required iron, and the iron stores may be rapidly created, which would take months to achieve by the oral route. This shortens hospitalization.

Adverse reactions to parenteral iron: Each intramuscular preparation may cause local pain at the injection site, skin discoloration and local inflammation with tender regional lymphadenopathy. The systemic toxicity which may develop within 10 minutes of injection includes headache, fever, arthralgia, backache, tachycardia, flushing, haemolysis and circulatory collapse. These effects are probably due to excessive amounts of free iron in the plasma. Iron sorbitol, in addition, may cause disorientation and temporary loss of taste.

Large doses of iron dextran have been reported to produce sarcomatous changes at the injection site in rats.

The urine of a person on iron sorbitol therapy turns black on standing, probably due to conversion of excreted iron into iron sulfide and the patient should be warned about this effect.

With intravenous therapy, the systemic reactions are similar to those observed following intramuscular iron but can be severe. Anaphylactoid reactions can occur within the first few minutes of administration. Severe chest pain, respiratory distress, circulatory collapse and even death have been reported. In general, local inflammatory reactions are much less frequent with intravenous than with intramuscular iron. Conversely, shock or cardiac arrest is more frequent with intravenous iron administration.

TREATMENT OF ACUTE IRON POISONING

(a) A stomach wash with 1% sodium bicarbonate solution should be administered to remove undissolved iron tablets. The lavage should not be carried out later than 1 hour after ingestion of iron for fear of perforation.

(b) With the tube still in place, 1 per cent solution of sodium bicarbonate or preferably an iron binding chelating agent like *desferrioxamine* mesylate (5 to 10 g. in 100 ml. isotonic saline), calcium diethylene triamine pentaacetate (DTPA 35 to 40 mg./kg.) or calcium dissodium edetate (35 to 40 mg./kg.), should be administered to retard the absorption of iron from the gastrointestinal tract. The use of dimercaprol (B.A.L.) is contra-indicated as it forms a toxic complex with iron.

(c) Early replacement of body fluids and electrolytes using isotonic saline, correction of metabolic acidosis and hypotension by using ringer lactate and vasopressor agents, respectively, are indicated.

(d) An intravenous infusion of *desferrioxamine* is given in the dose of 20 mg. per kg. body weight in saline every 6 hourly or 1-2 g. intramuscularly every 3-4 hours, for 24-48 hours.

(e) Barbiturates, paraldehyde and other anti-convulsants may be necessary to control convulsions.

DESFERRIOXAMINE (Desferal): This compound, obtained from *Streptomyces pilosus*, is a potent and specific chelator of iron. It readily binds ferric iron to form ferrioxamine, a stable and water soluble chelate. Ferrioxamine is excreted 2/3 in the urine and 1/3 in the bile. It colours the urine reddish brown. *Desferrioxamine* also removes iron from hemosiderin except that in the bone marrow. One hundred milligrams of *desferrioxamine* bind 8.5 mg of iron.

The drug is generally well tolerated. Rapid intravenous injection can produce hypotension, tachycardia and allergic reactions in the form of erythema and urticaria. Allergic reactions and

cataract formation are known to occur during its chronic administration in the treatment of iron storage diseases. The drug is contraindicated in patients with severe renal disease or anuria, and in pregnant women.

The drug is available as lyophilized powder (500 mg) for solution. It is administered by intravenous or subcutaneous infusion and by intramuscular injection.

Therapeutic uses:

(i) **Acute iron intoxication:** In this condition, *desferrioxamine* is used along with other measures including induced vomiting, airway maintenance, gastric lavage with either sodium phosphate or sodium bicarbonate, and treatment of shock and metabolic acidosis. In severe cases (in shock), the drug is administered by intravenous infusion: 10 mg/kg/hr for the first four hours, followed by 5 mg/kg/hr for the next 8 hours, and then 2-5 mg/kg/hr till the serum iron falls to 100 μ g per 100 ml. The rate of infusion should not exceed 15 mg/kg/hr; and the total daily dose should not exceed 240 mg/kg (6g/24 hrs). In less severe cases (without shock), it is given intramuscularly in the dose of 40 mg/kg every 4-12 hours.

(ii) **Hemochromatosis:** *Desferrioxamine* is useful in the prevention and treatment of iron overload in patients with chronic anemia treated with multiple transfusions. In these patients, it is administered by continuous i.v. or s.c. infusion in the dose of 2 g over a period of 12 hours once daily. Concomitant administration of ascorbic acid (0.5 to 1 g twice a day) improves the chelating action of the drug. Intramuscular bolus administration is less effective.

The drug is less effective than phlebotomy in primary hemochromatosis, but may be used when phlebotomy is contraindicated.

D.T.P.A.: The calcium salt of D.T.P.A. (Diethylenetriamine penta-acetic acid), which bears structural resemblance to E.D.T.A., is employed orally and parenterally in acute iron poisoning. It is administered by intravenous infusion, initially in the dose of 2.5 g., followed by 4.0 g. on each

of the successive days. The drug is almost completely excreted in urine in 34 hours. Mild side effects such as nausea, vomiting and diarrhoea are occasionally encountered. The drug is also employed in the treatment of hemochromatosis.

ADJUVANTS TO IRON THERAPY

Various substances claimed to enhance the efficacy of iron are vitamin C, cobalt, copper and manganese. Vitamin C may increase the iron absorption but it is not necessary to use costly iron preparations incorporating vitamin C to achieve this effect. Copper is said to mobilize iron from storage, while cobalt is claimed to stimulate erythropoietin production. Cobalt is potentially toxic. Angina, goitre and congestive cardiac failure are some of the adverse effects reported with the use of cobaltous chloride. The therapeutic value of these agents in the treatment of iron deficiency anemia is doubtful.

In the treatment of pure iron-deficiency anemia, the use of 'Shotgun' therapy containing a wide variety of expensive minerals and vitamins along with iron is unnecessary and wasteful.

ERYTHROPOIETIN AND ANEMIA

Anemia is an almost invariable feature of chronic renal failure. It is most severe in anephric patients. The critical defect is probably inadequate secretion of erythropoietin, the major hormonal regulator of red cell production, produced principally by the kidney.

The gene coding for human erythropoietin has now been cloned and recombinant human erythropoietin, purified from the cell-condi-

tioned medium, is now available. Preliminary studies indicate that patients treated with erythropoietin can achieve near normal hemoglobin levels despite the metabolic effects of chronic renal failure and routine hemodialysis.

ERYTHROPOIETIN has molecular weight about 36,000. It is a glycoprotein hormone mainly produced by the kidney, and is probably synthesized in response to hypoxia. Some amount of erythropoietin is produced by the liver, which is the most important source of erythropoietin to maintain erythropoiesis in patients that are anephric or have degenerated kidneys. The target cell for erythropoietin is the early erythroid colony forming unit (erythroid). Several pharmacological agents such as thyroxine, growth hormone, prolactin, testosterone, beta 2 adrenergic agonists, PG's and angiotensin II stimulate the erythropoietin production, while alkylating agents, estrogens and beta-adrenergic blocking drugs inhibit its production. It is metabolised primarily in the liver.

The anaemia of chronic renal failure is characterised by normochromic, normocytic, hypoproliferative anaemia and it causes persistent debility. The main cause of anaemia appears to be inadequate production of erythropoietin by the kidneys. Human erythropoietin has now been prepared by recombinant DNA technology. Clinical trials indicate that it is useful in correcting the anaemia of end stage renal disease in patients maintained on haemodialysis. Thus, the need for transfusion is avoided. The hormone is given i.v., twice weekly (dose 75-450 IU/kg body weight weekly). The drug appears to be non-immunogenic and well tolerated.

31 Drugs Effective in Megaloblastic Anemias

The story of megaloblastic anemias really began in the middle of the nineteenth century when Thomson Addison, a physician from Guy's Hospital, London, described pernicious (deadly) anemia, so designated because of its fatal outcome. The brilliant discovery by Minot and Murphy in 1926, demonstrating the dramatic effectiveness of liver preparations in pernicious anemia, forms one of the landmarks in the history of therapeutics. This was followed by the work of Castle (1932) who postulated the hypothesis that 'an intrinsic factor' from the normal human gastric juice reacts with 'an extrinsic factor' in the food to produce 'antipernicious anemia principle'. Crystalline vitamin B₁₂ was isolated from the liver in 1948, almost simultaneously by Rickes and his associates in America and Smith and his co-workers in Great Britain and soon after, the 'extrinsic' factor and 'antipernicious anemia principle' in Castle's hypothesis were shown to be vitamin B₁₂. Another anti-anemic factor from the liver, useful in macrocytic anemia of pregnancy, was isolated in 1943 and identified as pteroyl-monoglutamic acid, which turned out to be the same as 'folic acid' described by Mitchel and co-workers in 1941 and so named by them because of its isolation from the leafy vegetable, spinach.

Megaloblastic anemia: Megaloblastic anemias are characterised by the presence of abnormally large, nucleated, red cell precursors, known as megaloblasts, in the bone marrow. A megaloblast is viewed as an example of the unbalanced growth between the cytoplasm and the nucleus due to improper and defective synthesis of nucleoproteins. In almost 95 per cent of the cases with megaloblastic bone marrow, vitamin B₁₂ and/or folic acid deficiency is present.

Although folic acid and vitamin B₁₂ influence different metabolic pathways in the synthesis of

nucleoproteins the final result of deficiency of either of these is defective DNA (deoxyribonucleic acid) synthesis. Since DNA is present in every cell, the basic abnormality affects all proliferating cells such as those in buccal cavity, tongue and gastrointestinal tract leading to glossitis, stomatitis and intestinal malabsorption. Other organs affected include the cervical and vaginal squamous epithelium, the ovary and testes. The precursors of white cells (giant metamyelocytes) and those of platelets show abnormal mitotic activity. These abnormally large cells give rise to abnormally large offsprings that appear in the peripheral blood, which shows fully haemoglobinized (hyperchromic), large, red cells called macrocytes, polymorphonuclear leucocytes with hypersegmented nuclei and giant platelets. The anemia is thus described as 'macrocytic hyperchromic'. Such abnormal cells have shortened life span and may undergo early haemolysis, which sometimes gives rise to associated jaundice. The anemia is also associated with leucopenia, neutropenia and thrombocytopenia. Vitamin B₁₂ deficiency may cause damage to myelin in peripheral nerves, spinal cord and brain. With folate deficiency, the loss of body weight is much more marked and nervous instability may be present; but, the damage to the myelin is doubtful.

Although the megaloblastic anemia due to vitamin B₁₂ and/or folic acid deficiency produces peripheral macrocytosis, not all the macrocytic anemias are megaloblastic. Thus, the macrocytic anemias due to liver disease, myxedema, following certain hemolytic states, some aplastic anemias and leukemias usually have normoblastic bone marrow; these obviously do not respond to vitamin B₁₂ and/or folic acid.

Physiological role of Vitamin B₁₂ and folic acid: Physiologically, both these vitamins are

closely related and play an important role in the synthesis of nucleoproteins. The deficiency picture produced by both is clinically indistinguishable except that the neurological disturbances are commoner with vitamin B12 deficiency than with pure folic acid deficiency; the peripheral blood picture and bone marrow changes are also similar and only certain special tests and blood levels of these vitamins give the correct clue about the precise diagnosis.

Small 'physiological' doses of either folic acid or vitamin B12 will selectively improve the blood picture only in those persons suffering from a deficiency of the particular vitamin being administered; large 'pharmacologic' doses of either vitamin, however, will cause a hematological response irrespective of the type of deficiency, vitamin B12 or folic acid or both.

The physiological functions of vitamin B12 are still not well understood. Although it is believed that folate deficiency may lead *directly* to megaloblastic anemia, such a direct effect is doubted in case of vitamin B12. It is established that coenzyme vitamin B12 is essential in the activity of various enzyme systems, but only a few of such enzyme systems have been shown to occur in animal and human tissues. Since the deficiency of one vitamin is known to affect the metabolism and utilisation of the other, it is possible that vitamin B12 produces its actions *indirectly* by influencing folate metabolism and megaloblastic anemia produced by vitamin B12 deficiency is partly due to deranged folate metabolism.

COBALAMINS: Chemically, vitamin B12 belongs to the family of cobalamins which are cobalt containing carrinoid compounds. Cobalamins are dark red crystalline hygroscopic powders, readily soluble in water. The solution is stable at room temperature. These compounds differ from each other in the groups attached to the cobalt atom. In case of cyanocobalamin, a cyanide group is attached to the cobalt atom. A cobalamin with hydroxy (OH) group linked to the cobalt atom is known as hydroxocobalamin.

Cyanocobalamin, on exposure to light, is converted to hydroxocobalamin, while hydroxocobalamin in the presence of cyanide gets changed into cyanocobalamin. Other cobalamins of physiological importance are aquocobalamin, nitrocobalamin, methylcobalamin and 5'-deoxyadenosine coenzyme.

Only cyanocobalamin and hydroxocobalamin are used therapeutically. They are discussed below under the general heading 'Vitamin B12'. They differ in their metabolic handling by the body.

VITAMIN B12: Vitamin B12 is synthesized solely by micro-organisms in soil, water and animal intestine or rumen. It is almost entirely absent from plant products. In man, as in animals, this vitamin is synthesized in the colon by micro-organisms; however, it is hardly absorbed from this site and hence, is excreted (about 3-5 µg daily) in feces. Some of the animals like rabbit and rat eat their own feces (coprophagy) and hence, they have very high serum vitamin B12 levels. Nonvegetarian foods like muscle, liver, kidney, oysters, fish and egg yolk are rich in vitamin B12. Dairy food contains smaller amounts of vitamin B12. The vitamin B12 content of cow's milk is considerably more than that of human milk.

The daily dietary intake of this vitamin varies considerably and is high in non-vegetarians and likely to be very low in vegetarians, some of whom may not even consume sufficient amount of milk or milk products; however, vegetarians may obtain enough vitamin B12 from the water and in the form of co-enzyme B12 by ingesting legumes and nodules of root vegetable in which vitamin B12 is synthesized by micro-organisms.

The minimum daily requirement of vitamin B12 in adult man is not exactly known but it is believed to be extremely small, about 1 µg per day. Taking into consideration the incomplete absorption of the food B12, the recommended daily dietary intake is 2 µg for adults, 3 µg in pregnancy and lactation and 0.3 µg for infants.

Absorption of vitamin B₁₂: The cobalamins in food exist in a bound form and are metabolically inactive until they are released by heat (cooking) and by proteolysis in the stomach or intestines.

Vitamin B₁₂, given in microgram doses, such as are present in the diet, is absorbed only in the presence of intrinsic factor, produced by the parietal cells of the gastric mucosa. Thus, very little or none is absorbed in cases with pernicious anemia and after gastrectomy as the intrinsic factor is absent.

The nature of the intrinsic factor necessary for vitamin B₁₂ absorption is still a mystery but it is a glycoprotein. In man, it is produced by the fundus and the body of the stomach. The site of production differs in different species and it has a species specificity. Human gastric juice and most preparations of hog intrinsic factor do not promote the absorption of vitamin B₁₂ in gastrectomised rats. Further, it is antigenic and antibodies against intrinsic factor are known to develop.

The essential property of the intrinsic factor is its ability to bind vitamin B₁₂ and to act as a carrier. The presence of hydrochloric acid probably facilitates this binding in the stomach, which is essential for protecting the vitamin from getting firmly bound to other substances in the intestinal tract and thus escaping absorption. Many naturally occurring substances can also bind vitamin B₁₂ but they are not intrinsic factors. Intrinsic factor thus escorts vitamin B₁₂ to the site of absorption, which is ileum in man and facilitates its absorption. There is no evidence that intrinsic factor is absorbed into the plasma.

Ionic calcium is necessary for the initial binding of the intrinsic factor - B₁₂ complex to the ileal receptor site. Low ionic calcium concentration and a low pH as observed in chronic pancreatitis may cause vitamin B₁₂ malabsorption.

The maximum absorption of vitamin B₁₂ occurs within 8-12 hours following a physiological dose, and this appears to be uninfluenced by the concentration of vitamin B₁₂ in the blood.

Cyanocobalamin can also get absorbed with-

out the help of intrinsic factor, but the dose needed is in milligrammes. This type of absorption occurs by simple diffusion, probably by mass action. It is, however, inefficient as only 1.5 per cent of a 1000 µg dose is absorbed as compared to 90 per cent or more of 0.5 µg dose, in normal individuals. Absorption of hydroxocobalamin and deoxyadenosylcobalamin is considerably slower but their retention in the intestinal wall and in the tissues is more than that of cyanocobalamin.

Given subcutaneously or intramuscularly, cyanocobalamin is rapidly absorbed and the plasma level reaches the peak in 1 hour. Satisfactory absorption can also occur when it is administered by nasal insufflation or by aerosol inhalation.

Vitamin B₁₂ transport and storage: Absorbed vitamin B₁₂ is transported in the serum, bound probably to 2 globulin called transcobalamin II. Only 1-10 per cent circulates as a free fraction. The major form of vitamin B₁₂ in the serum is methylcobalamin attached to a globulin; this may be a circulating storage form of vitamin B₁₂. The total body stores of cobalamin in normal adult are estimated at about 2-5 mg., of which about 50-90% is present in the liver. Not all of this, however, is available for hemopoiesis.

Turnover of vitamin B₁₂ is very slow and in long-term studies only 0.2-0.3 per cent of the total vitamin B₁₂ contained in the body is excreted per day. Vitamin B₁₂ is excreted in the bile but most of it is reabsorbed, so that there is a closed enterohepatic circulation. This is how the body conserves vitamin B₁₂ and this would explain partly why even strict vegans with a very low intake of this vitamin do not commonly develop clinical vitamin B₁₂ deficiency syndrome. The lack of intrinsic factor or defective absorption due to intestinal pathology in such cases, however, will lead to a rapid depletion of vitamin B₁₂ stores.

Excretion: The daily urinary loss of vitamin B₁₂ is very small, ranging between 0 and 0.25 µg. Only the cobalamin not bound to proteins is capable of being excreted by glomerular filtra-

tion. Conservation of the vitamin by enterohepatic circulation and its very slow excretion explain why it takes a long time, perhaps 5-6 years, for deficiency to develop in the presence of deficient intake or absorption. The half life of a tracer dose of radioactive vitamin B12 in the liver is about 12 months.

If vitamin B12 is injected, only the amount necessary for the saturation of the binding sites is retained; the remaining excess is excreted in the urine. It is calculated that 80-95 per cent of a 50 µg dose of injected vitamin B12 is retained. As the dose exceeds 100 µg, large proportions (50-98%) of the injected dose may appear in the urine within 48 hours in healthy individuals.

Vitamin B12 crosses the placental barrier and the cord blood level of vitamin B12 in the newborn is significantly higher than the maternal blood levels.

Metabolic actions of vitamin B12: Cyanocobalamin itself has no metabolic activity in man. After absorption it is converted by cellular enzymes in a variety of tissues to the coenzyme forms which are active. Thus, it is converted to the naturally occurring coenzymes deoxyadenosylcobalamin and methyl-cobalamin. Although many reactions in bacteria are known to be B12 co-enzyme dependent, so far only a few of these have been demonstrated in man. Further, it should be noted that there are profound differences between the manifestations of vitamin B12 deficiency in man and experimental animals. Only the important metabolic actions and their probable relationship to abnormalities observed in humans are discussed below:

(i) Normally, during the conversion of homocysteine to methionine, methyl group from N⁵-methyl tetrahydrofolic acid (THFA) is first transferred to cobalamin to form methyl cobalamin. The methyl group from methyl cobalamin is then transferred to homocysteine to form methyl-homocysteine also called methionine. Lack of vitamin B12 affects indirectly the normal folic acid metabolism by causing a 'methyltetrahydrofolate trap'. This may explain the

similarity of gastrointestinal lesions as well as peripheral blood picture seen in megaloblastic anemia due to deficiency of either vitamin B12 or folic acid. Although methyltetrahydrofolate is the principal monoglutamic folate of liver and of serum, its conversion to other folate co-enzymes solely by the cobalamin-dependent methyl transferase is not yet established, and the methylfolate trap is still a hypothesis.

(ii) The cobalamins play a direct role in the biosynthesis of DNA in the micro-organism *L. leichmanii*. Such a direct role in the biosynthesis of DNA by mammalian tissue, however, has not been demonstrated.

(iii) The cause of the neurologic lesions in vitamin B12 deficiency in humans is obscure. The major pathway of propionic acid utilisation in animal tissues involves the conversion of propionic co-enzyme (CoA) to succinyl CoA. Thus, propionyl CoA is first converted to methyl malonyl CoA. Vitamin B12 CoA is necessary for the conversion of methyl malonyl CoA to succinyl CoA. Deficiency of this enzyme interferes with the production of lipoprotein in myelin tissue and may explain the neurological complications such as peripheral neuritis, optic atrophy and subacute combined degeneration of the spinal cord. However, direct proof for this hypothesis in humans is lacking.

(iv) Vitamin B12 is concerned with the maintenance of sulphhydryl group (SH) in reduced form, which is necessary for the function of many SH activated enzyme systems. In vitamin B12 deficiency in man, there is decreased availability of reduced SH compounds, mainly glutathione, in the erythrocytes and the liver. This is corrected by vitamin B12 therapy.

(v) Human red blood cells have low folate stores in the presence of vitamin B12 deficiency. The red cells folate rises after B12 therapy, suggesting that B12 plays some role in folate uptake and storage.

(vi) In B12 deficiency in man, there is inadequate production of myelin which is a lipoprotein. Co-enzyme B12 is probably involved in

linking fat and carbohydrate metabolism. It is necessary in protein synthesis, in hemopoiesis and also wherever nucleoprotein synthesis occurs.

(vii) It has been demonstrated in animals that supplementing the diet with vitamin B12 has a growth promoting effect. It is used in poultry farming for increasing the bird weight and for fattening the pigs. No such growth acceleration effect, however, has been observed in normal or premature human infants.

Administered parenterally, vitamin B12 does not seem to have any other significant pharmacological actions, even in large doses.

Assay of vitamin B12 and blood levels: It can be assayed chemically but the chemical assay is not very sensitive. Vitamin B12 in biological samples is assayed microbiologically using *Euglena gracilis* or *Lactobacillus leichmanii* as the test organism. The serum level in normals consuming non-vegetarian food varies between 140 and 750 pg./ml. The levels in healthy subjects consuming vegetarian food are considerably lower, some of them even below 100 pg./ml.; they do not, however, show any clinical or haematological evidence of deficiency. The factors controlling the levels of serum vitamin B12 and folic acid are unknown. Although vitamin B12 deficiency anemia is accompanied by low serum levels, it is doubtful whether a low serum level of vitamin B12 necessarily signifies tissue deficiency in otherwise healthy subjects. Plasma vitamin B12 can also be assayed by using a radioisotopic competitive protein binding assay.

Preparations and dosage:

(i) Cyanocobalamin injection I.P. contains 100 µg of the anhydrous compound per ml.

(ii) Hydroxocobalamin injection contains 100, 500 or 1000 µg of the compound per ml.

(iii) Vitamin B12, either alone or with intrinsic factor, is also available for oral therapy. Relatively large doses have to be administered by the oral route to achieve an adequate response.

Adverse reactions: No adverse reactions have been reported following even large doses of cyanocobalamin. The injections are almost pain-

less. Allergic reactions to cyanocobalamin are doubtful and very rare.

Therapeutic uses:

(1) It is used in the treatment of megaloblastic anemia due to vitamin B12 deficiency due to :

(a) **Deficient intake** in nutritional megaloblastic anemia as seen in strict vegans. As the daily vitamin B12 requirement is extremely small, nutritional deficiency due to pure vitamin B12 is uncommon even among the vegetarians in India. Majority of the nutritional megaloblastic anemias observed in India are mainly due to folic acid deficiency. The nutritional vitamin B12 deficiency can be corrected by parenteral administration of vitamin B12.

(b) **Impaired absorption** of Vitamin B12 as observed in pernicious anemia (due to lack of intrinsic factor), after gastrectomy or resection of small bowel, in malabsorption syndromes and in gastrointestinal diseases involving stomach and intestine such as malignancy and tuberculosis. In all these conditions, absorption of orally administered radioactive vitamin B12 is markedly diminished. Correction of this absorption defect by simultaneous administration of intrinsic factor suggests its absence as observed in patients with pernicious anemia. This forms the basis for *Schilling's test*. In all these cases, vitamin B12 should be given *parenterally* as it is not significantly absorbed when given orally.

Hydroxocobalamin is the drug of choice. Initially, it is given in the dose of 200-1000 µg I.M. daily for 1-2 weeks to replenish the body stores. Then, a similar dose may be given I.M. once a month. The reticulocyte response occurs on 3rd to 4th day and reaches the peak by 5 to 8 days. In patients with pernicious anemia and in cases with incurable gastrointestinal lesions, the treatment has to be continued lifelong.

Infestation with the fish tapeworm also causes megaloblastic anemia due to preferential uptake of dietary vitamin B12 by the worm. This is not common in India but heavy infestation with other worms may possibly contribute to such a deficiency.

(c) **Inadequate utilisation of vitamin B12** which may occur in infants who inherit the deficiency of certain enzymes necessary for conversion of vitamin B12 to its co-enzyme forms.

(2) **Vitamin B12 neuropathies** such as tropical neuropathy, subacute combined degeneration, tobacco and tropical amblyopia, which sometimes occur without clearcut megaloblastic anemia, respond to parenteral vitamin B12 therapy. The exact mechanism of action is not known, but an interesting hypothesis has been put forward. There is some evidence to suggest that certain well defined neurological and ophthalmic syndromes may represent the chronic neurotoxic effects of cyanide, and that hydroxocobalamin may help in the detoxication of cyanide by binding it.

Vitamin B12, given in massive doses, has been claimed to be effective in such varied conditions as infective hepatitis, sterility, psoriasis, multiple sclerosis, herpes zoster, toxic amblyopia and trigeminal neuralgia; there is no clear evidence to suggest that this vitamin is of any value in such conditions. Nor there is any conclusive evidence to suggest its usefulness in patients with mental disorders.

HYDROXOCOBALAMIN: Hydroxocobalamin, when injected, is absorbed slowly from the injection site and is more protein bound than cyanocobalamin. The drug is excreted much more slowly and hence, higher blood levels are maintained over a longer period than with cyanocobalamin.

FOLIC ACID (PTEROYLMONOGLUTAMIC ACID): Folic acid occurs as yellow, spear shaped crystals. Its disodium salt is soluble in water in the concentration of 1.5 µg. per cent. Chemically, folic acid molecule contains pteridine, para-aminobenzoic acid and glutamic acid. It is named folic acid because it is commonly present in green leaves. The term 'folate' is used in the generic sense and includes other chemical forms.

Folate is present in abundance in green vegetables, liver and yeast. Moderate amounts are present in eggs, meat, fish and dairy foods. Most of the folic acid in vegetables is in conjugated form, where one or more glutamic acid molecules are incorporated in the structure. These are usually triglutamic and hepataglutamic acid conjugates. Prolonged boiling of food during cooking destroys most of the folate in the food. As in the case of vitamin B12 many microorganisms including those in the colon synthesize folic acid. It is doubtful, however, whether the folic acid synthesized in the colon is available for utilisation in man.

Absorption: Folic acid conjugates are hydrolysed to pteroylmonoglutamic acid by enzymes known as conjugases. Conjugases are present in vegetable and mammalian tissues. A conjugase is found throughout the gastrointestinal mucosa and in pancreas, the highest level being in the duodenum and jejunum. Pteroylmonoglutamic acid is absorbed almost completely in the small intestine, particularly in the proximal portion. As in the case of vitamin B12 physiological doses (1 mg.) are absorbed by an active process while large doses can get absorbed by diffusion. Absorption of food folate as such, however, is incomplete. Further, inhibition of conjugase by certain drugs or its decreased concentration due to intestinal pathology may cause malabsorption of polyglutamates in the diet.

Transport, storage and fate: Given orally, folic acid appears in the blood within 30 minutes. It circulates in the plasma mainly as N⁵ methyl tetrahydrofolate. Probably, it is partly protein bound although the specific protein for the transport of folate has not yet been identified. Folic acid is distributed in all the tissues. Its exact metabolism and degradation in the body are not known.

The amount of folic acid excreted in the urine is dependent on the dose. Thus, only a small amount appears in the urine following ingestion of 0.1 mg. of folic acid, while almost 90 per cent is excreted after the ingestion of 15 mg. Folate

appears in the urine within 6 hours after ingestion, and excretion is complete within 24 hours.

Vitamin C protects the reduced product, tetrahydrofolic acid, from oxidative destruction. It also protects the folate in the food. Hence, food poor in vitamin C content is generally low in folate content as well. There is no evidence, however, that vitamin C in any way potentiates the therapeutic effects of folic acid in man.

The total body folate is estimated to be in the range of 5-10 mg. of which almost one-third is present in the liver mostly as methylfolate. Unlike vitamin B₁₂, folate gets selectively concentrated in the spinal fluid.

Folate is incorporated in red cells during erythropoiesis and the amount decreases only slightly during their life span. Red cell folate is, therefore, considered as a useful indicator of body folate status.

The exact daily requirement of folate in humans is not known; but it appears to be about 200 µg in adults, 100 µg for children and 300-400 µg in pregnancy and lactation. Since the net folate losses from the body appear to be about 50% of the amount ingested, the recommended daily intake is 400 µg for adults, 200 µg for children and 600-800 µg in pregnancy.

Metabolic actions of folate: Like vitamin B₁₂, folic acid is inactive as such. It acts as a precursor of various co-enzyme forms which are implicated in single carbon transfer reactions. Folate co-enzymes are involved in various metabolic reactions. The important reactions are:

(1) biosynthesis of purine and pyrimidine nucleotides,

(2) interconversion of certain amino acids, such as serine to glycine, homocysteine to methionine, and catabolism of histidine to glutamic acid, and

(3) incorporation of formate into the purine ring.

These reactions are necessary for the synthesis of nucleic acid.

Bioassay and serum levels of folic acid: Folic acid is estimated microbiologically, using *Strep-*

tococcus faecalis or *Lactobacillus casei* as test organisms, which utilise folic acid for their growth. However, the results obtained by using these different organisms or even with the same organisms from different laboratories may differ considerably. This is due to the lack of a universally accepted standard technic for its estimation. Low blood level of folic acid, in itself, cannot be considered as a definite indication of folic acid deficiency. Various other tests have been proposed for diagnosing folic acid deficiency but none of these is without fallacies.

Adverse reactions: Folic acid is almost non-toxic in man and no adverse effects have been reported except a rare and doubtful allergic reaction. Fantastically large doses in animals may give rise to precipitation of folic acid crystals in the kidneys. This, however, has not been observed in man.

Preparations and dosage: Folic acid is an orange yellow, microcrystalline powder, odourless and tasteless, only slightly soluble in boiling water. Folic acid tablet contains 5 mg. of the drug. Dose 5 to 20 mg. by mouth. It can also be given parenterally.

Therapeutic uses: Folic acid is used in the treatment of megaloblastic anemias due to folic acid deficiency. These are:

(1) **Nutritional megaloblastic anemia:** This is the commonest type of megaloblastic anemia in India and other tropical countries, and is mainly due to dietary deficiency because of undernutrition. Megaloblastic anemia of protein caloric undernutrition of infancy and childhood is mostly due to folic acid deficiency. Cooking habits involving prolonged boiling of food with spices, which destroys folic acid, and possibly loss of folate in sweat contribute further to the development of its deficiency. It must be realised that wherever there is deficiency of folate there is also a lack of other nutrients and the ideal treatment lies in correcting the diet. Supplementation with folic acid orally can, however, avoid and correct this deficiency.

(2) **Anemia due to increased requirements:**

The commonest type of megaloblastic anemia in pregnancy is due to folate deficiency caused by the increased requirement both by the foetus and the mother particularly during the third trimester. Deficiency of folate during pregnancy is so common in India that prophylactic use of folic acid along with iron from the second trimester till the end of lactation is probably justified. Daily oral prophylactic dose of 300 to 500 µg of folic acid with about 100-200 mg. of elemental iron is all that is needed. In the treatment of established anemia, folic acid is usually given in a dosage of 10-20 mg. daily, although a dose of 5 mg. seems to be adequate. The drug can also be used intramuscularly.

Increased demand for folic acid has also been observed in various pathological states like leukemia, hemolytic anemia, chronic infections and in carcinomatosis; this is probably due to rapid cell synthesis. This may add to or aggravate the already existing anemia.

(3) Anemia due to impaired absorption: This is commonly observed in malabsorption syndrome associated with tropical sprue, extensive organic disease of the jejunum and in blind loop syndrome.

In other types of malabsorptive states such as idiopathic steatorrhea, adult celiac disease or nontropical sprue, sensitivity to the gluten fraction of wheat protein is often the offending cause. In such cases and in gluten enteropathy in children, administration of gluten free diet can give dramatic results; many patients in this group, however, also suffer from folic acid deficiency. In all these conditions folic acid is given parenterally in a dose of 15 mg. daily, followed by oral therapy as soon as the diarrhoea is corrected.

(4) Anemia due to impaired utilisation: Certain anti-epileptic drugs like phenobarbitone, phenytoin and primidone may cause folic acid deficiency anemia probably by competing with the normal metabolic activities of folic acid, because of their structural similarities. Drugs like methotrexate, the anti-malarial pyrimethamine and the antibacterial drug trimethoprim can also

cause folate deficiency by blocking the conversion of folic acid to tetrahydrofolate. A supplement of folic acid, 5-15 mg. daily, orally, can correct this deficiency. The antiepileptic treatment, if required, need not be stopped.

(5) Certain other megaloblastic anemias as in liver disease, chronic alcoholism and in scurvy are usually associated with folate deficiency.

Folate deficiency as a cause of neuropathy is not universally accepted, although cases of encephalopathy giving rise to a confusional state, usually diagnosed as senile dementia and/or myelopathy, responding to folic acid have been reported. Hence, folic acid may be tried empirically in obscure chronic neurological disorder not responding to B12 therapy.

Administration of folic acid alone is contraindicated in pernicious anemia as, although it may correct the hematological abnormality, it precipitates or worsens the neurological complications. The precise reason for this phenomenon is not known. It has been suggested that the administration of folic acid accelerates the utilisation of the meagre vitamin B12 stores in an already deficient subject and may thus produce further deficiency of vitamin B12 which is essential for maintaining the integrity of the central nervous system and the peripheral nerves. In a few cases of pernicious anemia, however, the folate stores are also so low that there is only little response to vitamin B12 therapy until folic acid is also administered.

FOLINIC ACID (Citrovorum factor): This is the term used for N⁵ formyl tetrahydrofolinic acid. It was originally found in the liver and was demonstrated to have a growth promoting effect on the organism *Leuconostoc citrovorum*. It is available in 1 ml. ampoules containing 3 mg. of the vitamin. Its only use is in the treatment of toxicity due to folic acid antagonists like methotrexate.

LIVER PREPARATIONS: Crude liver extract owes its activity to the presence of both vitamin B12 and folic acid, while highly purified

liver preparations contain mainly vitamin B12. Liver preparations played an important role in the treatment of megaloblastic anemias before the development of folic acid and vitamin B12. Being a biological product, liver extract is not very stable, its effect is less prompt and it is costly. The injection is painful and can give rise to allergic reactions which could be severe. Orally, these preparations are not so effective and often not palatable. Because of their lower efficacy and other disadvantages, liver preparations are no more advocated in the treatment of folic acid and vitamin B12 deficiency anemias. Liver extract, however, may be of some value in an occasional case of megaloblastic anemia resistant to other forms of therapy.

'Shotgun' antianemia preparations: The use of antianemic preparations containing multiple ingredients like liver, iron, folic acid, vita-

min B12, copper, cobalt and manganese must be deplored for various reasons. Some of these ingredients are unnecessary, wasteful and only increase the cost of therapy. Mixed therapy can also cloud the clinical picture and may delay the accurate diagnosis of the underlying disease. Thus, a favourable response to vitamin B12 in a case of megaloblastic anemia secondary to gastrointestinal pathology may foster false security and may thus obscure the correct diagnosis. The danger of giving folic acid with inadequate vitamin B12 stores in case of undiagnosed pernicious anemia has already been pointed out. Patients with pure iron deficiency anemia respond to iron administration and an addition of vitamin B12 or folic acid is not justifiable. Moreover, it should be noted that whenever a commercial preparation contains multiple ingredients in a mixture, most of these ingredients are usually present in inadequate amounts.

32 Drug Induced Blood Dyscrasias

In addition to blood loss caused by salicylates and allied drugs, various types of blood dyscrasias may occur following the use of certain drugs in toxic doses or sometimes even in therapeutic doses. These reactions can be grouped into three main categories.

(a) those due to impaired production of blood cells e.g. aplastic anemia.

(b) those due to increased destruction of blood cells e.g. hemolytic anemias, and

(c) those due to derangement of blood cell functions e.g. methaemoglobinemia.

The important drug-induced blood dyscrasias are as follows :

Drug-induced anemias: Megaloblastic anemias following certain drugs have already been discussed in Chapter 31. Drugs responsible for this can be grouped as follows:

I. Folic acid inhibitors,

(a) *DHF reductase inhibitors or folic acid antagonists:* Methotrexate, Pyrimethamine, Trimterene, Trimethoprim and Diamidine compounds.

(b) *Associated with impaired absorption and/or utilization of folic acid:* Phenytoin, Primidone, Barbiturates, Cycloserine, Alcohol, dietary amino acids glycine, serine, homocysteine, methionine and probably oral contraceptive agents.

II. Associated with vitamin B₁₂ malabsorption: PAS, Colchicine, Neomycin and Alcohol.

In addition, pyridoxine responsive anemia has been described in man. It is a hypochromic microcytic anemia, with normal serum iron, and bone marrow showing normoblastic, erythroid hyperplasia. The anemia is probably due to inability of iron to get incorporated into hemoglobin. The anti-tuberculous drug isonicotinic acid hydrazide causes such a type of anemia and neuritis, which respond to the oral administration of pyridoxine.

Agranulocytosis: In this condition, specific depression of leucocytes, particularly granulocytes, occurs. Drugs known to produce this condition do so relatively frequently, in 1 in 1000 to 1 in 100 of patients. Certain drugs like amiodipyrine and dipyrone produce agranulocytosis by an immune mechanism, where patient's serum with specific antibodies lyses granulocytes in the presence of the drug. However, with drugs like phenothiazine and antithyroid compounds the exact mechanism is not known. Drugs that are commonly known to produce agranulocytosis are listed in Table 32.1.

Periodic blood counts may not necessarily help to detect this danger before an infection develops. Patients taking such drugs, therefore, should be warned about unexplained fever, or infection such as sore throat with ulceration of mucous membrane, and should be instructed to report immediately. In this condition, the mortality rate is more than 20 per cent, mainly as a result of infection, which thus needs prompt treatment with appropriate antibiotics such as penicillin. Blood transfusion may be necessary. Pentonucleotides have been tried but are not of much value.

Thrombocytopenia: This is a less frequent complication and in most cases is due to immune mechanisms. This can be demonstrated by mixing fresh normal blood with the patient's serum containing an appropriate concentration of the drugs, where clot retraction is prevented. Quinidine is most commonly involved in causing this reaction. Other drugs known to produce thrombocytopenia are quinine, sulfonamides and related drugs (tolbutamide and chlorothiazide), digoxin, rifampicin, meprobamate, penicillamine and amphotericine. In addition, all drugs causing aplastic anemia could also cause thrombocytopenia.

Aplastic anemia: This is the most severe type

of blood dyscrasia; fortunately, it is rare. The evidence that a given drug is responsible for aplastic anemia in a given patient is largely circumstantial and in many cases toxicity may occur 2 weeks to 6 months after cessation of therapy. It is associated with pancytopenia and hypocellular bone marrow. The mortality is very high (more than 50%) and recovery, if it takes place, occurs only after prolonged illness for many months or even a year. The important offenders in this group are phenylbutazone, oxyphenbutazone, amidopyrine, idomethacin, antineoplastic drugs and the antibiotic chloramphenicol. Other drugs reported to produce aplastic anemia are mephenytoin, gold salts, potassium perchlorate, benzene, insecticides like DDT, gamma benzene hexachloride, antithyroidal drugs, sulfonamides and sulfonylureas. This reaction is probably not dose related and may represent some form of idiosyncratic phenomenon.

Cytotoxic drugs used in cancer chemotherapy may cause aplastic anemia as an extension of their pharmacological action.

The treatment of aplastic anemia is essentially symptomatic, and includes blood transfusion, control of infection with proper antibiotics, maintenance of nutrition and prevention of hemorrhage. Proper nursing is essential. The outcome, on the whole, is disappointing and the only way to guard against this dangerous complication is to use the drugs known to cause aplasia judiciously and only when absolutely necessary. Bone marrow transplants have been tried with limited success. Although glucocorticoids such as prednisolone (20-40 mg/day) do not induce a remission, they may control the hemorrhage. Androgens may sometimes produce a remission and their use is worthwhile. The dose should be large: testosterone enanthate 200-600 mg. I.M. weekly or fluoxymesterolone 30-40 mg. orally, daily for 3-6 months. Virilization is a price which the patient may have to pay for the saving of life.

Drug induced haemolytic reactions: These reactions occur generally with the drugs which oxidize hemoglobin.

Normally, the red cells contain the enzyme

Table 32.1 : Some drugs known to cause leucopenia, agranulocytosis and hemolytic reactions

Drugs causing leucopenia and agranulocytosis	Drugs causing hemolytic reactions
Tranquillizers : Chlorpromazine and related drugs, Meprobamate	Antibacterial agents: Sulfonamides, Furazolidone, Nitrofurantoin, Chloramphenicol
Analgesics : Amidopyrine, Phenylbutazone, Oxyphenbutazone, Analgin, Indomethacin	
Antibacterial agents : Chloramphenicol, Sulfonamides, Streptomycin Cotrimoxazole	Antileprosy drugs (sulfones) : Diaminodiphenyl sulfone, Sulfoxone
Antithyroid drugs : Thiouracil, Propylthiouracil, Methimazole, Potassium perchlorate	Antimalarials : Primaquine, Pamaquine, Mepacrine, Quinine
Miscellaneous : Troxidone, Procainamide, Thiacetazone, Gold preparations, Impiramine.	Miscellaneous drugs : Acetanilid, Salicylates, Phenacetin, Naphthalene, Water soluble analogues of vitamin K, Methyl dopa.

glucose 6-phosphate dehydrogenase. Normal functioning of G-6-PD is necessary for maintaining glutathione in its reduced form, which in turn protects the red blood cells from the damage by oxidizing agents. The drug-damaged red cells show precipitated denatured hemoglobin within the cell, identified as Heinz bodies in an appropriate blood smear preparation.

Individuals whose red cells are deficient in glucose 6-phosphate dehydrogenase (G-6-PD), reduced glutathione (GSH) or glutathione reductase are obviously more susceptible to drug induced hemolysis. Such deficiency is hereditary in nature. G-6-PD deficiency is known to occur predominantly in Negro males and to smaller extent in females. It is relatively rare in white population. Its presence has also been noted in Indians.

It must be realized that a hemolytic reaction with the oxidant drugs can occur even in normal individuals without G-6-PD deficiency, if the concentration of the drug is sufficiently high. The drugs which are commonly known to give rise to hemolytic reactions are listed in Table 32.1. Similar reactions can also occur due to improper functioning of phosphogluconate dehydrogenase and glutathione reductase.

Drugs can also cause hemolysis by an immune mechanism, where the red cell destruction is caused by circulating antibodies. Drugs which have been reported to cause immune hemolytic

anemia are penicillin, methyldopa, quinine, quinidine, stibophen and phenacetin. Patients with abnormal hemoglobins may develop hemolysis if they are given sulfonamides or 8-aminoquinoline drugs. The treatment of hemolytic reactions is essentially symptomatic. Glucocorticoids such as hydrocortisone may produce beneficial effects in blood dyscrasias caused by immune mechanisms.

Drug induced methemoglobinemia: The oxygen carriage by red cell hemoglobin is dependent on the availability of haemoglobin iron in the ferrous form. Drugs such as phenacetin, sulfonamides, bismuth subnitrate, ammonium nitrate and nitrites are known to oxidize the hemoglobin iron from ferrous to ferric state and thus cause methemoglobinemia. Infants below 6 months are more susceptible to this reaction, probably on account of a low concentration of the erythrocyte enzyme nicotinamide adenine dinucleotide (NADH) which normally reduces methemoglobin to hemoglobin. This enzyme is also genetically deficient in certain subjects who are more prone to develop drug-induced methemoglobinemia.

Treatment consists of stoppage of the drug and the administration of methylene blue which is an effective antidote. A dose of 50 ml of 1 per cent solution is usually administered by the intravenous route.

Section IX : Water, Electrolytes and Drugs Affecting Renal Functions

33 Water, Sodium, Potassium and Hydrion Metabolism

Water constitutes the major portion of the human body mass. Thus, in an average adult male and female, 60 and 51 per cent of body mass respectively is water; in a month old infant, 77 per cent of body mass is water.

Distribution of body fluids: Body fluids are broadly divided into:

(1) fluids inside the cells (intracellular fluid-ICF) and

(2) fluids outside the cell wall (extracellular fluid -ECF).

As pointed out by Robinson and McCance (1952), ECF is like the continuous phase while ICF is like the dispersed phase of an emulsion. ECF being continuous plays an important role as a transport medium for various substances moving into and from the cells, while the restriction of ICF in cells provides the basis for individual cellular functions.

The extracellular compartment is further divided anatomically, by the traversing blood vessels, into intravascular (containing plasma) and extravascular (or interstitial) moieties. Physiologically, however, these compartments are continuous in respect of their electrolyte composition, as small molecules and ions can easily cross the capillary walls. The main difference between these two fluids is in their protein content which is lower in the interstitial fluid.

The fluid present in the CSF, tracheobronchial tree, aqueous humor, the lumen of the gastrointestinal tract and certain glands, sometimes designated as the transcellular fluid, constitutes about 2.5 per cent of total body water.

The total body water can be measured by determining the volume of distribution of a

substance which, when given intravenously, gets evenly distributed throughout the body water. Heavy water (deuterium oxide) and radio-active tritiated water are ideal for this purpose; chemicals like urea and antipyrine have also been used.

The ECF can be measured by finding out the dilution of a known amount of an injected substance which distributes itself through ECF without entering the cells. Thiocyanate, inulin and sucrose are commonly used for this purpose. The intravascular or plasma volume can be measured by similar dilution technic employing radioiodinated human serum albumin (RIHSA) or Evans blue (T-1824), which, when injected intravenously, remains intravascularly and does not escape into the interstitial fluid. The ICF volume is assessed indirectly, by subtracting ECF volume in litres from the total body water in litres. Of the 60 per cent total body water in an average young individual weighing 70 kg., about 33 per cent is present in the intracellular compartment, while only 27 per cent is present in the extracellular compartment, of which plasma water constitutes 4 per cent.

Body fluids contain various substances, some of which are vital for normal functioning of life. Some of these exist as ionized particles carrying a positive or a negative charge. When placed in an electrical field, they migrate to the cathode (cation) or the anode (anion); hence they are known as *electrolytes*. The electrolyte composition of ECF is distinctly different from that of ICF. Thus, sodium, chloride and bicarbonate are mainly extracellular while potassium, magnesium, phosphate and sulfate are essentially intracellular. The electrolyte composition of plasma

Table 33.1: Electrolyte structure of plasma and intracellular fluid

	Plasma mEq/l	I.C.F. mEq/kg intracellular water
Cations		
Na	142	11
K	4.5	164
Ca	5	2
Mg	3	28
Anions		
Cl	103	-
HCO ₃	27	10
PO ₄	2	105
SO ₄	1	20
Protein	16	65
Organic acids	6	5

Based on the results of Litchfield and Gaddie (1958), and on the literature. (Black D.A.K., Essentials of Fluid Balance, 4th Ed., 1967, Blackwell Scientific Publications. The table is reproduced by courtesy of the Author and the Publishers.

and intracellular fluid is given in Table 33.1

There are, however, certain similarities between these two compartments. Thus, in each compartment the total cation concentration in milliequivalents (m. equiv.) is almost same as the total anion concentrations in m. equiv. (Table 33.1). Both fluids are, therefore, very nearly electrically neutral. Further, the total electrolyte concentrations of these two compartments are not grossly different. However, the differences, such they exist, are essential for the specialized functions carried out by them.

Functions of electrolytes:

(1) *Maintenance of osmotic pressure:* The amount of water present in a given compartment is determined by the number of particles present, exerting an osmotic effect. Electrolytes play a major role in maintaining osmotic pressure. It is the number of molecules or ions and not the total mass of a solute per unit volume of fluid that determines its osmotic pressure. Substances with

low molecular weight possess a larger number of molecules per unit mass than substances with high molecular weight. Hence, although the plasma protein mass is very much larger than the plasma sodium mass, the latter contributes far more to the osmotic pressure of plasma than the proteins. Thus the biological functions of the electrolytes will be better understood, not by noting their concentration in mg. per cent but by some other unit which express the concentration in terms of molecules per unit weight of the solvent (i.e. molality). Molal solution is one which contains one mole of solute per 1000 g. of the solvent. One millimolal solution is also one milliosmolal. The osmotic balance between the I.C.F. and the E.C.F. is largely maintained by the electrolytes, whereas that between the E.C.F. and the intravascular compartment is largely determined by the osmotic effect of the plasma proteins.

Normally, the volume, the total electrolyte concentration and the osmolality of ECF are maintained within narrow limits. The normal osmolality of the plasma is about 300 milliosmoles per kg. of water and most of it is due to the electrolytes in the plasma. It is maintained constant by the kidneys. A rise in blood urea or glucose in some diseases, however, may increase the plasma osmolality significantly.

(2) *Maintenance of electroneutrality:* Electroneutrality of the body fluids is maintained by the concentrations of positively charged ions (Cations) and negatively charged ions (Anions) being nearly equal. In order to emphasize the concept of electroneutrality of the body fluids, it is customary to express the concentrations of electrolytes in terms of their chemically reactive units viz. milliequivalents rather than mg. per cent. The concentration in mg./100 ml. can be converted to m. equiv./l. by the formula:

$$\frac{\text{mg./100 ml.} \times 10}{\text{equiv. wt.}} = \text{m. equiv./l.}$$

As per new international System of Units (SI) the electrolyte concentration is now expressed as mmol./l instead of m. equiv./l.

(3) *In the production of energy*: Energy at the cellular level is produced by anaerobic and aerobic glycolysis and is stored in available form in high energy phosphate bonds. Intracellular potassium and magnesium are essential for the function of various enzymes necessary for this process. Inorganic phosphorus is necessary for ATP synthesis. Potassium depletion is known to affect various metabolic processes such as utilization of carbohydrates and synthesis of proteins. Weakness in chronic diarrhoea is attributed partly to potassium depletion. For effects of phosphorus depletion, see Chapter 65.

(4) *In impulse transmission*: The neuronal and the muscle activities are known to be associated with transmembrane shift of the electrolytes, with reversal of these during recovery period. Some drugs like dilantin sodium, quinidine and digitalis are known to modify these shifts of electrolytes and thus alter the cell functions.

(5) *Miscellaneous*: Electrolytes also have certain specialized functions to perform e.g. calcium in blood clotting and bone formation.

WATER METABOLISM

In health, the total body water content is usually well maintained within normal limits, although the water and electrolyte output may vary considerably from day to day. Water intake varies widely in subjects from different climates and even among the individuals from the same region. The daily water intake includes that taken as water, beverages and that in food. Approximately 300 ml. of water is produced daily in the body during oxidation of food. The output is mainly in the urine; in addition, about 100 ml. is lost in feces and about 1000 ml. in the expired air and through sweating. Considerable loss of water in sweat can occur in tropical countries like India. Under basal conditions, water balance can be calculated as follows: (24 hours intake + 300

ml. produced by oxidation of food) (24 hours urinary volume + 1000 ml. lost from skin and lungs). This obviously gives only a gross assessment but is useful in clinical practice.

In individuals from the tropics, the total body water on body weight basis and the water turnover are more than in those from the temperate zones. The amount of water lost by insensible perspiration is also likely to be more, particularly in hot and dry climate where the heat loss occurs mainly by evaporation of water from the skin and very little heat can be lost by radiation. Water lost in hot but humid climate is somewhat less because of less evaporation from the skin.

The rate of sweating in terms of body mass is greater in children upto age of 9 months than in adults. This is probably necessary as the metabolic rate of infants is about twice that of adults.

Acclimatization to heat reduces the volume of sweat produced at a given temperature, probably increases the threshold for the onset of sweating and also reduces the volume of sweat produced for a given heat load. The local inhabitants of tropics, therefore, produce 30 per cent less sweat from a unit skin area in a saturated hot environment than unacclimatized Europeans.

In health, water balance is maintained by (i) intake as regulated by thirst and (ii) output in urine as regulated by antidiuretic hormone (ADH). The exact stimulus for the production of thirst is not known. Thirst can be induced not only by water depletion but also by increasing salt intake. It is well known that one feels thirsty after eating excessively sweet or salty food. Water depletion leads to increase in ECF sodium level. Such an increase in extracellular solute concentration may cause extraction of water from the cells. Thus, evidence has been presented to indicate that the cellular dehydration caused by water deficit or an increase in extracellular solute concentration acts as an effective stimulus to thirst. However, factors other than cellular dehydration may also modify this response. A thirst centre has been demonstrated in goats and existence of a

similar central mechanism has been proposed in man.

The output of water in the urine is mainly controlled by the ADH. It has been demonstrated that increased plasma osmolality caused by water depletion activates the osmo-receptors in the hypothalamus, which in turn stimulates the release of ADH. In the normally hydrated man, plasma ADH levels are around 4μ units per ml. and may rise up to 21μ units per ml. during dehydration. The antidiuretic hormone promotes water absorption in the distal tubules of the kidney, thus reducing the urine volume and increasing its osmolality. The body, thus, tries to conserve water. However, other stimuli like pain, decrease in blood volume or ECF, psychological disturbances, drugs like morphine, nicotine and barbiturates are also known to increase ADH release.

Both these mechanisms, thirst and ADH activity, are very sensitive even to small changes in the osmolality of body fluids. They are, however, less influenced by changes in the volume alone. In the natural stress of water deprivation these two mechanisms act synergistically and thus protect the body from excessive water depletion. Water excess is essentially countered by inhibition of ADH release, resulting in a decrease in water resorption by the kidney tubules, leading to water diuresis.

Water metabolism is intimately connected with the changes in solute content of the body. Thus, an increased intake of solutes necessitates increased water intake, and increased retention of sodium is associated with retention of water causing edema. Similarly, an excessive loss of solutes in the urine causes an increased water loss (osmotic diuresis).

The adreno-cortical hormone aldosterone also influences the water balance, mainly by modifying the sodium metabolism. Physiologically, hydrocortisone, another hormone of the adrenal cortex, is essential for eliminating an extra load of water from the body. In its absence as in case of Addison's disease, patients are unable to ex-

crete the water load adequately. This forms the basis of 'Water Load Test' in the study of adreno-cortical function.

Water depletion: The clinical syndrome of water depletion is usually associated with disturbances of electrolyte metabolism as well; selective water deficiency is not common. Relative water deficiency, which is common, can occur:

(a) due to reduced water intake in patients with extreme lethargy or coma,

(b) in gastrointestinal disorders with defective water absorption,

(c) due to excessive sweating as in fever; hypotonicity of the sweat causes a greater loss of water than of sodium,

(d) in certain cases of chronic renal failure,

(e) in diabetes insipidus and in certain intracranial lesions, where there is a deficiency of ADH.

Infants, in general, are more prone to develop water depletion than adults, as the kidneys of infants are unable to concentrate the urine adequately.

The clinical syndrome of water depletion can occur either due to pure water deficiency or due to increased body electrolyte contents. Both these factors cause increase in body fluid osmolality.

In mild water depletion the osmolality of body fluids increases as their volume is decreased. This decrease in the volume is initially spread evenly over all the fluid compartments. Marked diminution of volume, however, stimulates the secretion of aldosterone causing sodium retention which conserves the ECF volume in preference to ICF.

Clinical history helps the clinician to suspect water depletion in a given case. Such a patient is usually apathetic and confused. The urine volume is markedly reduced except in conditions like diabetes insipidus or chronic renal failure. The plasma sodium, proteins and blood urea levels are raised; but as the loss of fluid from the plasma is associated with a corresponding loss of fluid from the erythrocytes the hematocrit percentage is not significantly raised. A conscious

patient usually complains of thirst, dryness of mouth and difficulty in swallowing. Severe water depletion causes unconsciousness and finally even respiratory failure. In practice, the clinical picture of water depletion is usually complicated by the associated sodium depletion.

The treatment is to give enough water, which, in the presence of normal kidney function, is well tolerated. In patients who are vomiting and unconscious, water in the form of 5 per cent glucose is given intravenously, as the solution is isotonic with blood. This also supplies calories and prevents ketosis. Associated disturbances in electrolyte concentrations should be corrected. Patients with fever and polyuria obviously need more water.

In the absence of thirst, the water requirement can be judged by noting the 24 hour urinary volume and plasma sodium concentration. After adequate water supplement, the former rises and the latter decreases to normal levels.

Patients on high protein intake need more water to prevent water depletion.

Water excess: This is not so commonly seen as water depletion, but can occur following unrestricted administration of fluids in the presence of inadequate urinary output. In mild cases, the patient may develop headache, nausea, vomiting and mental confusion. Body weight increases and edema may occur. Severe water intoxication can produce convulsions and coma. The plantar response may be extensor and pupils unequal. The symptomatology of water intoxication is probably due to hypotonicity of body fluids with resultant cerebral edema.

The presence of oliguria, in spite of adequate hydration of subcutaneous tissues, low serum sodium level, and an awareness on the part of physician that such a possibility may exist, help to diagnose the water excess.

The treatment of water intoxication consists of restriction of intake of non-saline fluid. In severe cases with convulsions and coma, 50 to 100 ml. of 5 per cent saline is given intravenously, repeatedly, till the plasma sodium is raised to about 130 m. equiv./l. Isotonic saline is not useful in water intoxication as it does not help to raise the serum sodium level.

In patients with renal disease with oliguria, water intoxication must be avoided by restricting the intake of water as guided by the urinary output.

SODIUM METABOLISM

The study of sodium metabolism is fundamental to the understanding of electrolyte physiology. Prolonged deprivation of sodium in animals can result in death, and marked physiological disturbances are known to occur in man following either sodium deficit or excess.

Sodium distribution: Sodium is present principally in ECF, though this is not its only important location. The distribution of body sodium is shown in Fig.33.1. Besides ECF, there is a considerable amount of sodium in bones, which act as a sodium reservoir. The total body sodium can be measured by (i) direct carcass analysis and (ii) isotope dilution technic using radioactive sodium. The radioactive sodium, when injected intravenously, gets uniformly distributed in all the body fluids and tissues containing stable sodium, except some portion of the bone; the distribution is proportional to the stable sodium content of various compartments and body tissues. This process is known as 'sodium exchange'. Since plasma represents the ECF, by noting the dilution of injected radiosodium in the plasma, 'body exchangeable sodium' can be calculated by the formula:

Exchangeable body sodium m. equiv. =

$\frac{\text{Radiosodium injected} - \text{Radiosodium excreted}}{\text{Radiosodium/m. equiv. of plasma sodium}}$

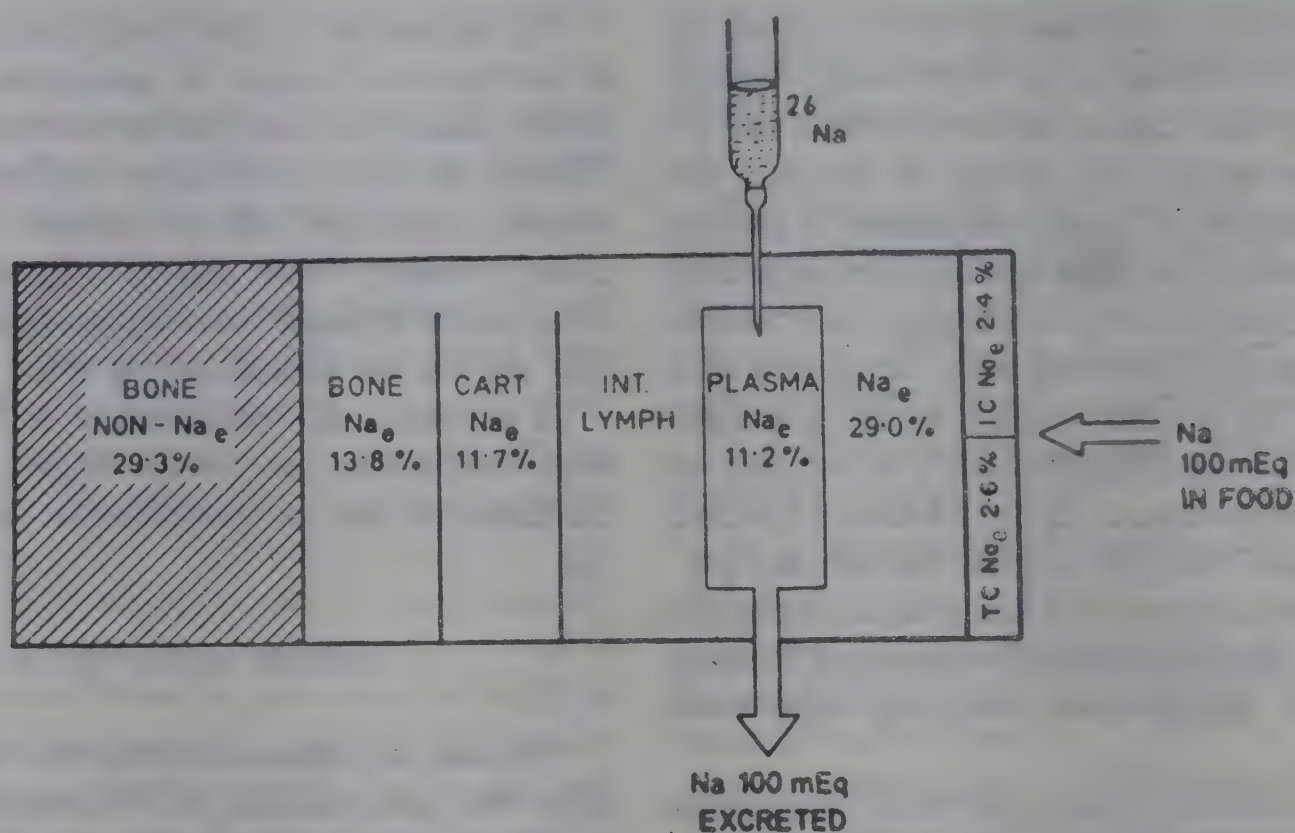


Fig. 33.1 : Distribution of body sodium. Note that a considerable amount of sodium is in the bone and is not exchangeable with radiosodium within 24 hours of equilibrium. T.C.: Transcellular; I.C. : Intracellular; Cart. : cartilage.

Body sodium calculated by this method is approximately 45 m. equiv. per kg. in Indian males and about 43 m. equiv./kg. in Indian females. Thus, an average Indian male weighing 60 kg. will have 2700 m.equiv. of exchangeable sodium. This value, however, is less than 'actual total body sodium', as some part of the bone sodium is not estimated by isotope dilution technique, using 24 hours equilibrium period. Estimation of exchangeable sodium is commonly used in studying the sodium metabolism in preference to elaborate sodium balance studies which are more laborious and may involve cumulative errors. Although the exchangeable sodium may vary over a wide range, the serum sodium level is maintained remarkably constant in health at 140.9 ± 4.8 (S.D.) m. equiv./litre.

Body content of sodium over a long period depends on the balance between intake and output. The daily intake of sodium varies considerably between 50 and 500 m. equiv. Unlike the phenomenon of thirst, no craving for salt is observed in sodium depletion; and hence, exces-

sive sweating in tropics can easily cause salt depletion producing the symptoms of 'heat exhaustion'. Sodium loss in stools is very small. This may, however, be very marked in diarrhoea and cholera. The major output of sodium occurs in the urine; the urinary sodium output varies considerably, even on a constant diet. In tropical countries, the loss of sodium in sweat can be considerable, particularly with occupations that involve physical exertion. Sweat contains less sodium per litre than plasma. The sodium content of sweat in infants is 2.5 m. equiv./l, while in adults, not acclimatised to hot weather, it is 90 m. equiv./l. With acclimatisation, it is reduced to 10-15 m. equiv./l. Excessive sweating thus causes proportionately more water loss than sodium loss.

Although the rate of absorption of sodium and water from isotonic saline solutions is probably very similar in the human jejunum and ileum, there are important differences. Thus, the jejunum is capable of absorbing sodium chloride against slight concentration gradients only. It

appears that the sodium absorption in the jejunum occurs mainly by passive process. Experiments with human proximal jejunum suggest that (1) concurrent glucose or fructose absorption stimulates water absorption and that water movement across the mucosa stimulates passive absorption of sodium by 'solvent drag'; (2) glucose also stimulates active sodium absorption; (3) fructose, unlike glucose, stimulates active potassium absorption; (4) the sodium concentration in the jejunum is of critical importance in determining the rate of sugar enhancement of sodium absorption; thus, sodium absorption increases with rising intraluminal sodium concentration; and (5) bicarbonate absorption is an active process and increases with increasing intraluminal bicarbonate concentration; however, it is minimally affected by concurrent glucose or fructose absorption. In contrast to jejunum, in the ileum sodium can be absorbed against large concentration gradients and it is not affected by water flow nor by the addition of glucose or bicarbonate. It is believed that the sodium absorption in the ileum occurs mainly by active transport process. These findings have an important clinical application in oral fluid therapy (see management of cholera).

About 1000 m. equiv. of sodium are secreted daily into the alimentary tract. This is totally reabsorbed. Aldosterone is known to promote the absorption of sodium from the intestines and the colon.

Urinary excretion of sodium: Normally, about 13-20 m. equiv. of sodium is filtered out every minute at the glomeruli. Of this, over 98 per cent is reabsorbed by the renal tubules and only 2 per cent of the originally filtered load is excreted in the urine. Hence, even a slight interference with the tubular reabsorption mechanism can produce a marked increase in the urinary sodium loss. Increasing the amount of sodium filtered at the glomeruli has a less marked effect on urinary sodium. A decrease in the filtered load of sodium as in congestive cardiac failure, however, leads to sodium retention and edema; failure of the tubules to reabsorb sodium due to

lack of aldosterone causes marked sodium depletion as in Addison's disease.

Excretion of sodium in the urine is regulated by (1) renal blood flow, which depends upon cardiac output, local condition of the kidney vessels, and plasma and ECF volumes and (2) hormonal control particularly by aldosterone, which influences tubular reabsorption of sodium.

Hormonal control of sodium metabolism: The bulk of sodium filtered by the glomeruli is reabsorbed in the proximal tubules independently of hormonal control. However, the adrenal salt retaining steroids are involved in the final control of sodium balance. Aldosterone is perhaps the most important natural hormone which promotes sodium reabsorption and potassium excretion, by acting on distal renal tubules. The action of aldosterone is not limited to kidneys alone but it is known to modify the sodium concentration of sweat, saliva and intestinal juices. It also probably plays a part in regulating the movement of sodium and potassium across the cell membrane. The aldosterone secretion is believed to be regulated by (1) a reflex pathway with a regulatory centre in the brain which responds to changes in serum electrolytes such as sodium depletion, potassium loading or to ECF volume changes such as blood loss or reduction in body water. With respect to volume receptors, two have been clearly established and stimulation of either the right atrial wall or the juxta-glomerular apparatus in the kidneys can alter the secretion of aldosterone, and (2) a humoral mechanism related to renin-angiotensin system with its trigger in the kidney. In normal man, sodium depletion increases while sodium loading decreases the plasma renin levels. The Yanomamo Indians inhabiting the tropical rain forests of Brazil, who do not use salt in their diet and thus have life-long very low levels of sodium intake, show elevation of plasma aldosterone and renin. Interestingly their blood pressure does not rise with age unlike in the developed world consuming a lot of salt. Chronic elevation of renin without hypertension probably indicates the

importance of the level of body sodium in affecting blood pressure in man. The renin-aldosterone system, however, does not fully account for the physiological mechanism involved in the renal handling of sodium. Recent evidence suggest the presence of a circulating humoral material which decreases tubular sodium resorption, an effect opposite to that of aldosterone.

The myocytes of right and left atria synthesize and release a 28 amino acid peptide, now fully synthesized, which has a potent naturetic effect (Atrial Natriuretic Polypeptide, ANP). Pharmacologically, in addition to a direct action on the renal tubules, it inhibits angiotension II induced aldosterone secretion by the adrenal cortex, causes inhibition of renin secretion by the kidneys and causes renal vasodilation. Its plasma levels rise whenever the right atrial pressure is elevated e.g. in patients with congestive heart failure, in chronic renal failure and in patients undergoing dialysis. Some patients with essential hypertension also have elevated ANP levels. More potent and longer acting analogues of ANP are being developed in the hope that they could be used in the therapy of salt retaining states such as congestive heart failure.

Other hormones like hydrocortisone, oestrogens and testosterone can also produce sodium retention. Adrenaline and noradrenaline may

affect sodium metabolism indirectly by their actions on blood vessels. ADH has no direct effect on sodium metabolism. However, in the syndrome of inappropriate ADH secretion (SIADH), expansion of plasma volume leads to natriuresis, probably through inhibition of aldosterone secretion. The marked sodium loss that occurs in diabetic ketoacidosis is due to increased glucose concentration of ECF with resultant polyuria.

The customary quantities of salt in contemporary diets far exceed the amount necessary to maintain sodium balance in health and this results in depressed levels of sodium related hormones, renin and aldosterone. It thus becomes apparent that salt intake in humans is generally not a true reflection of salt requirement.

SODIUM DEPLETION

True sodium depletion is one in which there is actual loss of sodium from the body. This must not be confused with the 'low salt syndrome' characterised by low plasma sodium concentration (hyponatremia). In this 'low salt syndrome' the total body sodium may not necessarily be low.

The effects of pure sodium depletion are distinctly different from those of pure water depletion. During the early stages of sodium depletion,

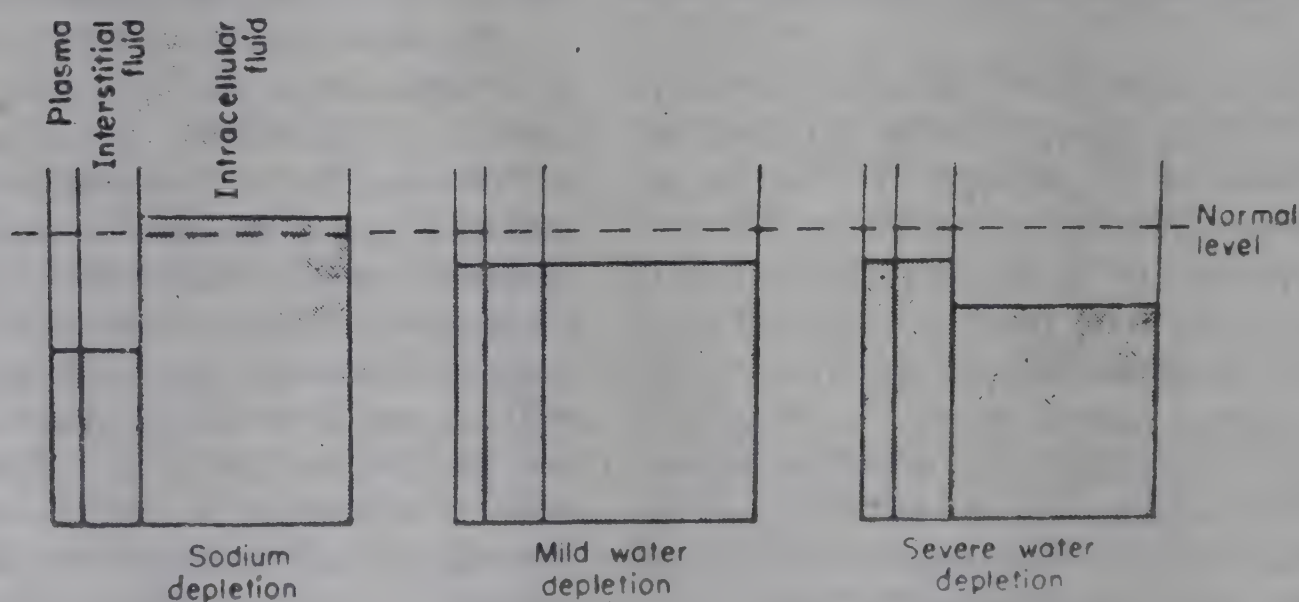


Fig. 33.2 : Effect of sodium depletion and of mild and severe water depletion on the partition of fluid between E.C.F. and I.C.F. (Black D.A.K., *Essentials of Fluid Balance*, 4th Ed. 1967, Blackwell Scientific Publications. The figure is reproduced by the courtesy of the author and the publishers)

the filtered sodium is almost completely reabsorbed. In addition, an excess of water is excreted by the kidneys, producing dilute urine. Nature, thus, tries to preserve serum sodium concentration at the cost of ECF volume which contracts. Bones release some of their sodium which helps to maintain the serum sodium level; such release is more marked in younger and sodium depleted acidotic animals. With further losses of sodium, the serum sodium level ultimately falls (hyponatremia). This may lead to further loss of ECF water, partly into urine and partly by a shift of water into the cells causing an increase in the volume and a decrease in the osmolality of ICF. This is in contrast to changes observed in severe water depletion, where the ECF volume and plasma volume are maintained at the cost of ICF volume, which diminishes (Fig. 33.2).

Sodium depletion thus causes decrease in ECF and plasma volume resulting in a rise in the hematocrit and the serum protein concentration.

Causes of sodium loss:

(1) **Gastrointestinal loss:** as in diarrhoea and discharge from fistulae. Sodium loss can be very severe in watery diarrhoea as occurs in cholera or acute bacillary dysentery. In such cases, it is also associated with loss of bicarbonate leading to acidosis.

(2) **Renal:** Urinary loss of sodium is observed following diuretics, in diabetic coma, and during starvation or increased catabolism of proteins. A primary renal disease like acute tubular necrosis during its recovery phase and salt losing nephritis may produce marked sodium loss. Sodium loss is not directly linked with the urine volume. It can occur in the absence of polyuria (e.g. Addison's disease); on the other hand, sodium excretion may be normal even in the presence of polyuria (e.g. diabetes insipidus).

(3) **Environmental:** Considerable losses of sodium can occur in people working in hot dry climate like deserts and in hot moist climate.

(4) **Miscellaneous:** Draining of ascitic fluid can also produce marked sodium loss.

Symptomatology of sodium depletion: Mild sodium depletion (100-200 m. equiv.) is common in tropical countries. Patients usually complain of loss of appetite, lethargy and cramps. Since sweat is hypotonic, drinking water without correcting the sodium loss would cause body fluid dilution, which is partly responsible for these symptoms.

Massive sodium loss such as 1000-1500 m. equiv. is usually accompanied by shock. There is a fall in blood pressure, with marked vasoconstriction in the skin and kidney vessels. Limbs are cold. Cardiac output is low and pulse rate is high, probably due to hypovolemia. Loss of tissue elasticity and turgor is characteristic of sodium depletion and is due to a decrease in the interstitial fluid content. Eyeballs appear 'sunken'. Symptoms like muscle cramps, anorexia and vomiting are probably due to relative body fluid dilution, as these are also seen in water intoxication.

Sodium depletion and kidneys: In mild sodium depletion, renal reabsorption of sodium is complete, so that further loss is prevented. There is no change in serum sodium level or glomerular filtration rate. The effect is mainly brought about by an increased aldosterone production, which promotes complete tubular reabsorption of filtered sodium.

In patients, in whom sodium loss continues by extrarenal routes, as in severe diarrhoea, the cardiac output falls which, in turn, reduce renal blood flow and GFR. The renal blood flow is further reduced because of active renal vasoconstriction. This causes a rise in blood urea and consequently extrarenal uremia. It is vitally important to distinguish this uremia from that following primary renal failure with sodium loss, as the former is reversible with proper treatment. In case of doubt, a therapeutic trial with saline infusion is justified. Primary sodium depletion can cause albuminuria but the presence of hematuria and casts is suggestive of intrinsic renal disease.

Sodium depletion following alimentary los-

ses is obvious. In other conditions, history and symptoms help to suspect it. The possibility of sodium loss from the kidney itself should be borne in mind.

In sodium depletion the serum sodium level may be low but presence of normal serum sodium does not rule out sodium depletion. In emaciated patients in whom clinical dehydration may be difficult to diagnose, estimation of blood urea may be useful, as this is raised in sodium depletion.

Treatment of sodium depletion: Mild degrees of volume depletion can be repleted by giving about 10 g. of sodium chloride and 2-3 litres of oral fluid daily. This can be done by administering adequate amounts of 0.9 per cent sodium chloride solution. The amount needed would vary, but moderately severe cases usually require about 3 litres. Overfilling of the neck veins indicates overloading with saline which should be avoided as it may cause pulmonary edema. Deficiency of other electrolytes, particularly potassium and bicarbonate, if present, should be corrected.

In patients with severe sodium and water depletion, the amount of isotonic saline needed is so large that if injected quickly, it may overload the circulation. Hence, slow intravenous infusion of hypertonic sodium chloride (3-5 per cent) solution is used for restoring plasma volume and renal circulation, particularly in patients with extrarenal azotemia. The hypertonic saline injected gets diluted by a shift of the water (which has entered into the ICF during severe sodium depletion) back to ECF. As severe sodium depletion is generally associated with acidosis, either sodium bicarbonate or sodium lactate has to be administered to correct the acidosis. (See later)

For subjects working in hot environment and in certain diseases like Addison's disease, where continued sodium loss is expected, prophylactic addition of sodium chloride to the diet is advisable.

Serum sodium level and total body so-

dium: It must be emphasized that although serum sodium may be low in cases with sodium depletion, not all patients with low serum sodium levels (hyponatremia) are suffering from body sodium depletion. In some of these cases with *hyponatremic syndrome* where plasma sodium level is low, the total body sodium may be normal or even high. Several factors are responsible for such a state.

Hyponatremia may be caused by:

- (1) primary sodium loss,
- (2) primary potassium loss,
- (3) primary water excess, or
- (4) combination of these.

Thus, hyponatremia in cases with gastrointestinal lesions is due to loss of sodium and potassium, while hyponatremia observed sometimes in edematous patient is due to loss of potassium and gain in total body water. In some cases it is associated with inappropriate ADH secretion. The treatment of hyponatremic states would, therefore, depend upon the cause.

SODIUM EXCESS

Increased sodium retention is always associated with water retention and this may manifest as pitting edema. Sodium excess due to increased intake is most unlikely to occur in the presence of normal kidney function. The main cause of retention of sodium is the failure of the kidneys to excrete the sodium load. This may be due to:

(1) intrinsic kidney disease e.g. acute nephritis,

(2) excessive reabsorption of sodium by the tubules e.g. in aldosteronism, and

(3) decreased renal blood flow such as in congestive cardiac failure and acute hypotension.

Estimation of serum sodium levels is not of much help in the diagnosis of body sodium excess and in fact, in some cases these may be even subnormal.

The treatment of sodium excess depends upon the cause which should be corrected, if possible. Therapeutically, sodium depletion can be

brought about by

(a) restricting the daily dietary sodium intake to 20-50 m. equiv.

(b) increasing the sodium output in urine by using diuretics. Diuretics are discussed in detail in Chapter 35.

(c) improving renal perfusion e.g. digitalis in congestive cardiac failure or intravenous infusions in oligemic shock.

Usually, these methods are combined.

Hypernatremia or increased serum sodium level is not necessarily associated with increased total body sodium. It has been observed that serum sodium correlates well with the osmolality of serum which is related to

$$\frac{\text{Exchangeable sodium} + \text{Exchangeable potassium}}{\text{Total body water}}$$

This observation in man provides a rational basis for the classification of hyper and hyponatremic states. Thus, hypernatremia may be due to:

- (1) primary sodium excess,
- (2) primary potassium excess,
- (3) primary water deficit, or
- (4) combination of these.

In practice, it is commonly due to excessive loss of total body water. It causes mental impairment in the adults.

Hypernatremia has been reported in a patient with perphenazine poisoning who was given 10 per cent hypertonic saline as emetic but failed to vomit, and in infants who were given feeds prepared with salt instead of sugar by mistake; half of these infants died. The clinical picture showed pyrexia, hyperpnea, hyper-reflexia and coma. Brain damage has been reported to be associated with hypernatremia due to heat stroke.

The treatment is directed towards reducing the serum sodium level. Since the majority of patients have diminished total body water and sodium, 5% dextrose in water should be given till serum sodium level has declined to normal. Thereafter, half normal saline is administered

until the salt deficit is corrected.

POTASSIUM METABOLISM

The total body potassium content can be estimated by

- (1) analysis of cadavers,
- (2) isotope dilution technic as described previously, and

- (3) measuring whole body radiation from the naturally occurring isotope of potassium ^{40}K .

Of these, isotope dilution technic is the most commonly employed method as it is convenient. The body potassium in man, as measured by isotope dilution, amounts to about 45 m. equiv./kg. in males and 38 m. equiv./kg. in females. These figures are lower than the actual total body potassium as estimated by cadaveric analysis by about 15 per cent. The requirement of infants and growing children for potassium is relatively higher than that of adults.

Distribution of potassium: Potassium is essentially a cation of the cells and hence its distribution is related to the cell mass. Thus, about 70 per cent of the total potassium is in the muscles, about 20 per cent in the brain and large viscera while 10 per cent is present in the skin and subcutaneous tissues. As compared to sodium, the amount of potassium in the bone is small, estimated at about 218 m. equiv.

The mean serum level of potassium is 4.5 m. equiv./l \pm 0.46 (S.D.). Although this is considerably lower than the mean serum sodium level, changes in serum potassium concentration can produce profound effects on body functions. Disturbances due to altered potassium metabolism can, therefore, be studied by noting the effects following changes in (a) total body potassium and (b) serum potassium levels.

Potassium intake and excretion: The daily intake of potassium varies considerably and is estimated to be about 50-150 m. equiv. It is likely to be more in vegetarians than in non-vegetarians as vegetables and fruits (citrus fruits, tomatoes, bananas) contain large amounts of potassium.

The major loss of potassium occurs in urine. Unlike sodium, potassium is secreted by kidney tubules. Thus, urinary potassium is not derived from the potassium filtered by the glomeruli which is totally reabsorbed, but is derived mostly from tubular secretion. It is known that the kidney reabsorbs sodium and, in exchange, excretes H^+ and K^+ ions in the distal tubules (Berliner mechanism). The normal urine is, thus, acidic in reaction. Because of this tubular secretion of potassium, the urinary loss of potassium would continue and may even be greater than the intake, when daily intake of potassium is restricted below 14 m. equiv. Increased sodium intake increases the potassium loss because it makes more sodium available for exchange with potassium while low sodium intake reduces the urinary loss of potassium.

Normally, about 5-10 m. equiv. of potassium are excreted in the stools. As in the case of urine, a part of this is secreted by the colon in exchange for sodium which is reabsorbed. This part of potassium loss in stools would continue even in subjects on potassium intake as low as 1 m. equiv. per day. This is contrast to body sodium which is conserved by achieving complete reabsorption of this cation by the renal tubules and the intestines, when sodium intake is markedly reduced.

The potassium concentration of sweat in infants is 3.9 m. equiv./l. as compared to the sodium concentration of 2.5 m. equiv./l. In nonacclimatised adults it is 10 m. equiv./l. Thus, proportionately more potassium is lost per unit volume of sweat than sodium, with respect to their plasma levels. Excessive sweating, as occurs during dry heat or during fevers, may cause significant potassium depletion.

Factors affecting plasma potassium: Since plasma is a part of the ECF, estimation of plasma potassium gives information about ECF potassium changes.

(1) Both sodium and potassium intake can modify plasma potassium. Thus, with normal intake of sodium, reduction of potassium intake would cause a fall in plasma potassium on ac-

count of continued loss of potassium in urine and feces. This may lead to potassium depletion.

(2) Increase in total body sodium causes loss of body potassium. Part of the retained sodium shifts into the cells, thus displacing some amount of potassium which is excreted. Conversely, in severe sodium depletion, as in diabetic coma, the serum potassium may be raised. It appears, therefore that changes in the ECF volume may cause a rise or a fall in serum potassium levels. In congestive cardiac failure, where sodium retention is marked and ECF volume is increased, the serum potassium level is usually low.

(3) Normally, the kidney tries to compensate for metabolic acidosis by secreting more H^+ ions than K^+ ions in exchange for sodium. This leads to potassium retention. Acidosis also reduces the potassium uptake by the cells. This may cause a rise in serum potassium level. If the plasma potassium level is high to begin with, acidosis will thus cause further rise in plasma potassium with resultant toxicity.

Acidosis, in the presence of marked potassium depletion, however, will cause severe cellular derangement as it will aggravate the fall of intracellular potassium.

Alkalosis is associated with lowering of plasma potassium level.

(4) Serum potassium levels are also affected by changes in the cell metabolism. Increased uptake of glucose by the cells is associated with a shift of potassium into the cell. This may cause a transient fall in serum potassium. In the presence of potassium depletion, such a shift may cause marked hypokalemia. This phenomenon occurs in patients recovering from diabetic coma where, as the tissue glycogen is repleted following insulin and glucose, potassium shifts into the cells thus causing a fall in serum potassium level. Protein anabolism is also associated with increased potassium uptake by the cells while protein catabolism would cause cellular potassium loss. In a condition called familial periodic paralysis, parietic attacks are associated with a shift of potassium from ECF into the cells.

(5) Diuretics and hormones like aldosterone, insulin and adrenaline are known to decrease plasma potassium. Their mode of action is discussed elsewhere. Agents like histamine, acetylcholine, tyramine and potassium salts can raise the plasma potassium.

POTASSIUM DEPLETION AND HYPOKALEMIA

The term hypokalemia is employed to denote a low plasma potassium level; this is usually associated with body potassium depletion. However, body potassium depletion can exist in the presence of serum potassium within normal range. It is believed that in an adult as much as 100 to 200 m. equiv. of potassium loss is necessary before the serum potassium shows a fall below 3 m. equiv./l.

Causes of potassium depletion: These can be grouped as follows:

(1) **Dietetic deficiency:** Potassium deficiency due to decreased intake occurs only rarely.

(2) **Gastrointestinal loss** (urinary K^+ equal to or less than 20 m. equiv. per day): This occurs in such conditions as vomiting of pyloric stenosis, copious discharge from a fistula, aspiration of intestinal contents and diarrhoea. In diarrhoea, both sodium and potassium are lost. In formed bulky stools, however, sodium loss may not be much but the loss of potassium could be considerable e.g. in steatorrhea and following chronic use of purgatives.

(3) **Renal loss** (urinary K^+ more than 30 m. equiv. per day): Increase in plasma potassium level due to intracellular potassium loss in such conditions as sodium overload, starvation, acidosis or protein catabolism increases renal loss of potassium. In addition, renal loss of potassium also occurs in:

(a) the presence of excessive aldosterone, hydrocortisone and excessive use of diuretics,

(b) extra-renal states like diabetic acidosis, and

(c) certain primary renal diseases such as renal tubular acidosis (Fanconi syndrome) and neph-

rotic syndrome.

Patients with glomerular diseases do not lose potassium; in fact, they generally retain potassium. However, potassium loss may be severe in some patients with renal tubular dysfunction. It must also be borne in mind that potassium depletion, in itself, may cause renal tubular dysfunction.

(4) Excessive sweating is also likely to be an important cause of potassium loss in the tropics.

Clinical manifestations: Since potassium is the major intracellular cation, its depletion is expected to produce widespread dysfunction. Mild potassium depletion, about 10 per cent of the total body potassium, does not produce any dramatic symptoms. Many vague symptoms are attributed to such marginal deficiency which is common. Thus, lethargy, malaise, weakness of muscular activity, anorexia and thirst have been attributed to but not definitely proved to be due to mild potassium deficiency.

Marked hypokalemia impairs neuromuscular function leading to paralysis, causes conduction defects in the heart, intestinal dilatation and even paralytic ileus, and lowers the blood pressure. Clinically, hypokalemia is associated with obvious arrhythmias and tachycardia. Tetany can also occur on account of ECF alkalemia.

Chronic cumulative loss of potassium secondary to renal or gastrointestinal dysfunction may cause nonspecific symptoms like muscular pain, abdominal distension and nocturia. If such a deficiency is not suspected, these symptoms may lead to the erroneous diagnosis of neurosis and may even result in death, if left untreated. It must be pointed out that there is no consistency in the symptoms for any given level of plasma potassium. In general, in severe potassium depletion plasma potassium level is below 3.5 m. equiv./l. except in cases with acidosis and associated sodium depletion.

In excessive potassium depletion, the capacity of the kidneys to concentrate urine is reduced. There is a reduction in urinary pH and an increase in ammonia secretion.

Loss of potassium in amounts greater than 30 per cent of the total body potassium causes widespread damage to cell function.

Renal lesions in potassium depletion: In animal experiments, potassium depletion has been shown to produce extensive histological changes in the kidney. The two principal lesions are:

(1) the cells of the most distal segment of the collecting tubules exhibit an intense droplet formation in their cytoplasm, and

(2) proximal to this, the cells in the corticomedullary region are hyperplastic. This may cause nephron obstruction and tubular dilatation and eventually nephron destruction and atrophy.

In patients with potassium depletion, renal cortical biopsies have shown cellular swelling and vacuolization. This renal tubular lesion is known as 'clear cell nephrosis' or 'vacuolar nephropathy'. It is doubtful, however, whether potassium deficiency alone ever produces serious renal failure; it may, however, cause deterioration in renal function when this is already reduced by the kidney disease.

Experimental studies in man have suggested that renal chloride conservation may be impaired and phosphate reabsorption reduced by K deficiency. On the other hand, renal ammonia production is increased.

Other changes: Potassium deficiency leads to retention of sodium. The neuromuscular abnormality is probably due to the abnormal resting membrane potential and subsequent alteration in the excitability. The skeletal muscle fibres may show Zenker's waxy degeneration. The normal activity of both skeletal and smooth muscles is impaired. The heart muscle may also show degeneration and even necrotic changes. The electrocardiogram in hypokalemia shows ST depression with prolonged QT interval and inversion of T wave. Prominent U waves may be seen.

Chronic potassium deficiency causes alkalosis by bringing about a shift in H ions from the extracellular space into the intracellular space in exchange for K ions.

The ability to form gastric acid and to absorb electrolytes from the bowel is impaired. Animals with chronic potassium depletion fail to grow.

Treatment of potassium depletion: Potassium should usually be given by mouth. Fruit juices and coconut water contain adequate amounts of potassium in palatable form; in addition, these also supply some calories. Fresh, green, coconut water contains about 70 m. equiv./l. of potassium. A single orange gives 8-10 m. equiv. of potassium, a tomato 16-22 m. equiv. and a banana 20-22 m. equiv. In the presence of normal kidney function, oral administration of adequate amounts of potassium is usually effective in controlling chronic potassium depletion with low serum potassium level.

Drug of choice is potassium chloride although potassium citrate is less unpalatable than potassium chloride or bicarbonate. Three grammes of potassium chloride gives 40 m. equiv. of potassium. The bad taste of the salt can be masked by adding a small quantity of ginger extract. Usually, a mixture is preferred to tablets as the latter have been shown to cause intestinal ulcerations.

In acute cases, potassium depletion is associated with other electrolyte disturbances such as sodium depletion and acidosis. These, along with the water depletion, should be corrected as discussed elsewhere. A vigorous correction of acidosis should be avoided as potentially lethal hypokalemia may be precipitated.

In emergency cases, potassium can be given intravenously by drip method; 40 m. equiv. of potassium per litre are recommended as a safe limiting concentration, with ordinary drip-rates (one litre in 3-4 hours). Such a concentration can be prepared by adding 20 ml. of potassium chloride injection B.P. to one litre of saline or glucose drip. During the intravenous infusion of potassium, the serum potassium level and electrocardiogram should be checked as a sudden marked rise in serum potassium may cause cardiac arrest.

Potassium should never be given directly into a vein or into the tubing of an intravenous infusion as this may cause sudden rise in serum K^+

level and death from cardiac arrest. Further, the serum K^+ level should be known and adequate urine output established before treatment.

Darrow's solution commonly used intravenously in diarrhoea in children, has the following composition:

Sodium chloride	0.4%
Sodium lactate	0.6%
Potassium chloride	0.27%

Potassium salts can also be used prophylactically in patients receiving digitalis and certain diuretic drugs that cause K^+ loss. In such cases, a daily supplement of 50-100 m. equiv. is adequate.

Alkalosis due to hypokalemia cannot be corrected except by potassium administration.

HYPERKALEMIA AND POTASSIUM EXCESS

Unlike the clinical syndrome of sodium excess, the syndrome of increase in total body potassium has not been definitely documented. Hyperkalemia or increase in the serum potassium level, however, is fairly common and may often cause fatal complications.

Causes of hyperkalemia: In the presence of normal kidney function, increased oral intake of potassium causes only a transient hyperkalemia. Usually, dangerous blood levels are not reached, unless potassium is injected intravenously, suddenly and in large quantities.

The most important cause of hyperkalemia is acute or chronic renal insufficiency. Occasionally, it can occur following tissue injury, due to increased catabolic processes, diabetic and chronic respiratory acidosis, in patients with Addison's disease due to lack of aldosterone, and following certain drugs like spironolactone and triamterene.

It should be noted that the plasma potassium in neonates is high and levels upto 10 m. equiv./l. may be observed without any obvious toxic effects.

Pharmacological effects of high serum potassium: It affects both cardiac and skeletal

muscles. It may cause various arrhythmias, idioventricular rhythm and finally, cardiac arrest in diastole, if the serum level exceeds 7 m. equiv./l. The ECG shows peaking or tenting of T wave, depression of ST segment and widening of QRS complex. PR interval may be prolonged.

Skeletal muscles may show paralysis. Ascending paralysis involving respiratory muscle has been described in hyperkalemia; this is probably due to a block in transmission in the muscle membrane as direct application of potassium to the muscle causes contraction.

Treatment of hyperkalemia: Serum potassium level can be reduced by (1) Avoiding potassium in the diet. This means that the daily caloric requirement is given mainly as carbohydrates and fats but no proteins; usually 400 g. of glucose are given daily orally along with limited water.

(2) Preventing tissue breakdown and promoting protein anabolism by using anabolic steroids, which may help to shift the potassium into the cells.

(3) Promoting the entry of potassium into cells by injecting 5-10 units of plain insulin and 50 ml of 50% glucose intravenously over 5 minutes and by correcting the acidosis. Sodium bicarbonate (45 m. equiv.) may be injected intravenously over a 5 minute period and repeated after 10-15 minutes if the E.C.G. abnormality persists. However, large quantities of sodium bicarbonate should be avoided. Many prefer a rapid infusion of 1000 ml. of 10% dextrose in water with 90 m. equiv. of sodium bicarbonate, one-third in 30 minutes and the rest in 2-3 hours, together with 25 units of plain insulin subcutaneously.

(4) Promoting potassium excretion by using glucocorticoids such as hydrocortisone in Addison's disease.

(5) Using cation exchange resins given orally for depleting potassium.

(6) Carrying out peritoneal dialysis or hemodialysis, and

(7) Controlling infection.

The toxic effects of high serum potassium on heart can be temporarily countered by giving

intravenous calcium gluconate, 5-10 ml. of a 10% solution, to be repeated after 5 minutes if necessary.

Every case of hyperkalemia needs proper assessment and planning of appropriate therapy to achieve reasonably satisfactory results. Hemodialysis offers the most effective and rapid method for correcting severe hyperkalemia and is many times life-saving.

ACIDOSIS AND ALKALOSIS

As discussed above, the body concentrations of sodium and potassium are important in the regulation of ECF and ICF volumes and their tonicity. The regulation of the reaction of the body fluids, however, is mainly influenced by their 'hydrogen ion' content now designed by the word "hydrion" $[H^+]$.

According to the present concept, an acid is a proton donor molecule or ion which provides a proton (hydrion H^+) a positively charged particle, and thus lowers the pH of a solution into which it is placed. This means that apart from conventional acids like HCl, other agents like ammonium ion which can split into a proton + ammonia or even water which can split to give a hydrion + a hydroxyl ion can be considered as acids. By this definition, chloride, sulfate and phosphate ions are not acids but considered as the conjugate bases of a true acid. On the other hand, a molecule or an ion which can accept a proton (hydrion) is termed as a base; it thus raises the pH of a solution into which it is placed. Thus, ammonia (NH_3) and hydroxyl (OH) ions are bases as they can accept a proton and produce ammonium (NH_4) and water respectively.

Water can act as an acid as well as a base, depending upon the circumstances. As an acid, it gives up a hydrion to yield OH ion, while as a base it can accept a hydrion to produce hydronium (OH_3) ion.

The metallic ions, by these definitions, are neither acids nor bases, as they do not provide any protons nor can they accept protons because

of their positive electrical charge. Thus, in a chemical reaction between NaOH and HCl, sodium and chloride ions do not take any active part but the hydrion from the HCl is transferred to the hydroxyl of NaOH to produce water.

Unlike the concentration of sodium and potassium, the body fluid concentration of hydrion is very small and can be measured using a pH meter.

In the plasma, CO_2 is present as carbonic acid ($H.HCO_3$) whereas bicarbonate (HCO_3) is present in combination with cations as $B.HCO_3$. Hence CO_2/HCO_3 ratio may also be expressed as $H.HCO_3/B.HCO_3$ ratio. If the concentrations of both carbonic acid and bicarbonate in the blood were fixed, the $[H^+]$ of the blood would also be fixed. Thus, in health the $[H^+]$ of blood is remarkably constant. The changes in the $[H^+]$ of the body fluids are resisted by three mechanisms: (1) buffer systems, (2) renal mechanisms and (3) respiratory mechanisms. Buffer mechanisms merely minimize disturbances when strong acids or bases are added to the blood but the blood $[H^+]$ is maintained constant at its normal value mainly by the combined efforts of kidneys and lungs. The respiratory mechanisms try to fix the carbonic acid concentration in the blood at 1.4 m. equiv./l. and the kidneys try to maintain the blood bicarbonate level at 28 m. equiv./l. The ratio of $H.HCO_3/B.HCO_3$ is thus fixed at 1.4: 28 resulting in a $[H^+]$ of 40 nanno equiv./l. Normally, the arterial plasma $[H^+]$ varies between 36-44 n. equiv./l. Since the pH of the solution is the negative logarithm of $[H^+]$ expressed in g. equiv./l., the normal pH of arterial plasma is calculated to be between 7.44-7.36. The remainder of the buffer systems in plasma then adjust the ratios of their acids to bases in keeping with this pH.

Unlike with sodium and potassium one cannot measure 'hydrion balance', as hydrion does not maintain its identity in the body; it is constantly disappearing or is constantly produced during various complex reactions of energy metabolism. Major portion of the body hydrion is produced during the oxidation of food and tissue metabo-

lism; the contribution made by the actual intake of hydrion is very little.

Metabolically, hydrion is produced in the body in two forms:

(1) '*Potential hydrion*' or as CO_2 , which is produced by the combustion of foods like carbohydrates, fats and proteins. This can normally be eliminated by the lungs. In the presence of respiratory diseases, however, retention of CO_2 raises the $\text{H}.\text{HCO}_3/\text{B}.\text{HCO}_3$ ratio and hence, increases hydrion concentration in the plasma, although the total body production of hydrion is not raised.

(2) *Non-volatile hydrion* which is derived from:

(i) Incomplete oxidation of carbohydrates and fats, giving organic acids,

(ii) Sulfuric acid, produced following the oxidation of sulfur containing amino acids, and

(iii) Phosphoric acid, produced following the oxidation of phosphoprotein residues.

The nonvolatile hydrion is normally excreted by the kidneys, mainly in the form of ammonium ion NH_4 (H^+ buffered by NH_3) and titratable acidity (H^+ buffered by HPO_4). Very little acid is excreted as free H ions.

The plasma concentration of hydrion being regulated mainly by the lungs and the kidneys is proportional to the plasma ratio CO_2/HCO_3 ; the level of plasma CO_2 is regulated by the lungs and the respiratory centre while HCO_3 level is regulated by renal conservation. Physiologically, effect of a sudden rise in plasma hydrion is countered by the action of blood and tissue buffers and to a certain extent by exchange of hydrion with bone cations. The renal adjustment, though important, is rather slow to occur.

The ratio $\text{H}.\text{HCO}_3/\text{B}.\text{HCO}_3$ and thus the blood $[\text{H}^+]$ can be disturbed by factors that change either the carbonic acid or bicarbonate levels in the blood. Thus, a fall in carbonic acid or a rise in bicarbonate level will decrease the ratio and the $[\text{H}^+]$ in the blood, leading to *alkalosis*. Similarly, a rise in carbonic acid or a fall in bicarbonate will increase the ratio leading to rise in the $[\text{H}^+]$, causing *acidosis*. In all the cases of

$[\text{H}^+]$ disturbances, when the fault is primarily respiratory the compensation is primarily renal and vice versa.

Table 33.2 gives the normal values of acid-base parameters in arterial blood.

Table 33.2 : Normal values of acid base parameters in arterial blood

Parameter	Normal range
pH	7.38 - 7.42
pCO_2 (mm Hg)	37 - 42
HCO_3 (mMol/L)	24 - 28
PO_2 (mm Hg)	85 - 100
SaO_2 (%)	98

In modern instruments, pH, PO_2 and pCO_2 are determined and SaO_2 and HCO_3 are calculated. The pH gives a quantitative idea of the acid-base balance of the extra-cellular space but only a qualitative idea of the total body acid-base balance. To obtain the latter an additional parameter called '*bicarbonate deficit*' is calculated.

$$\text{Bicarbonate deficit} = (\text{body weight} \times 0.6) \times (\text{Normal } \text{HCO}_3 - \text{Actual } \text{HCO}_3).$$

The term 'base excess' should not be used for this as it has been used in more than one sense and therefore, can be confusing.

The 'anion gap' is used to divide metabolic acidosis into those with normal anion gap and those with high anion gap. Normal anion gap is 10 - 18 mMol/l.

$$\text{Anion gap} = (\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-), \text{ all in mMol/l.}$$

The anion gap represents anions which are not normally measured in acid-base studies: proteins, phosphate, sulfate and organic acids. *Metabolic acidosis with normal anion gap* is due to bicarbonate loss from the G.I. tract or the kidneys; less commonly it is due to ingestion or infusion of HCl or a substance (NH_4Cl) effectively giving rise to it. *Anion gap is widened in* ketoacidosis, lactic acidosis, uremic acidosis and salicylate

poisoning.

ACIDOSIS

Acidosis is defined as an increase in either potential and/or nonvolatile hydrion *content* of the body. Increase in the hydrion *concentration* of the plasma is termed as *acidemia* and is manifested by a fall in pH of the blood. In certain instances, although excessive potential hydrion is produced in the body, the plasma level of hydrion may remain normal due to a compensatory increase in the ventilation. Such a state of acidosis without acidemia is known as 'compensated acidosis', which could become 'decompensated' if the metabolic cause remains uncorrected. Similarly in lung diseases, retention of potential hydrion CO_2 can be compensated by renal conservation of bicarbonate, thus maintaining the plasma ratio of $\text{H.HCO}_3/\text{B.HCO}_3$ constant. But this too would become 'uncompensated' if respiratory failure is not corrected.

Acidosis can occur as :

(a) **Metabolic acidosis:** This is due to excess production of hydrion in the body because of

(i) acceleration of the normal metabolic processes as during excessive catabolism in fever, starvation, dehydration and during diabetic ketoacidosis;

(ii) administration of drugs which are hydrion-donors e.g. salicylates, ammonium chloride or methanol;

(iii) excessive loss of alkaline fluids from the intestines, as in diarrhoea which causes a relative loss of hydroxyl (OH) ions;

(iv) administration of large quantities of normal saline;

(v) a high level of plasma potassium which results in a fall in plasma bicarbonate by interfering with the reabsorption and manufacture of bicarbonate by the kidneys; and

(vi) accumulation of lactic acid. This is seen in conditions like severe circulatory failure or following extracorporeal circulation where tissue hypoxia is present. Lactic acidosis is also seen

following oral hypoglycemic agents, biguanides, which inhibit aerobic glycolysis.

The rise in hydrion and fall in blood pH in metabolic acidosis are to a certain extent compensated by the buffering action of the blood and tissues, by increased ventilation and by increased renal excretion of the hydrion. Although hyperpnea and the buffering systems reduce acidemia they do not help to eliminate the excess of hydrion, which is solely excreted by the kidneys.

The net effect of metabolic acidosis is that the plasma bicarbonate and pCO_2 fall and urine becomes strongly acidic and has a high ammonium content.

(b) **Renal acidosis:** This is a type of metabolic acidosis, where increase in body hydrion is due to defective renal excretion of hydrion, either as titratable acid or as ammonium ion. This is seen either in selective tubular disorders (renal tubular acidosis) or in diseases primarily damaging the glomeruli (glomerulonephritis and diabetic nephropathy). Renal acidosis is also seen in Addison's disease where ammonia formation is inadequate. Carbonic anhydrase inhibitor drugs like acetazolamide which interfere with tubular secretion of hydrion can cause renal acidosis.

In renal acidosis the excretion of titratable acid and ammonium is impaired. The plasma bicarbonate and pCO_2 concentrations are low. The urine, however, may be alkaline.

(c) **Respiratory acidosis:** This is due to increased retention of the potential hydrion (CO_2) in the blood leading to a rise in plasma carbonic acid content. It usually occurs in chronic lung diseases with cor pulmonale, in diseases associated with respiratory muscle paralysis or following the respiratory centre depression by drugs.

Unlike in metabolic or renal acidosis, the plasma bicarbonate and pCO_2 are raised. The urine is strongly acidic. The associated hyperpnea may be difficult to differentiate from that due to original respiratory pathology.

Clinical manifestations of acidosis: The clinical picture is usually complicated by the associated electrolyte disturbances such as so-

dium depletion. Uncomplicated acidosis causes hyperpnea, muscle twitching and mental confusion. Patients with renal and metabolic acidosis may have Kussmaul breathing although they may not complain of dyspnoea. Ultimately, coma may result, which occurs more frequently in patients with respiratory acidosis; in such cases, the blood pH value is below 7.25. The diagnosis of acidotic coma is important as it is reversible following appropriate treatment. In patients with chronic acidosis, mental or respiratory changes may not be so prominent but the patient may complain of bone pains and tenderness due to demineralization of bones. X-ray of bones may reveal signs of osteomalacia and plasma alkaline phosphatase levels may be increased. This type of picture is usually seen in chronic renal acidosis.

Treatment of acidosis: In acute cases, other electrolyte disturbances like sodium and potassium depletion should be corrected and in many cases, this, along with the treatment of the cause, is the major form of therapy e.g. in diabetic acidosis and in diarrhoea. In moderately severe cases, acidosis can be corrected by a slow injection of 7.5% sodium bicarbonate in quantities sufficient (50-100 mEq. at a time) to raise the plasma bicarbonate concentration to about 15-20 mEq./l. No attempts should be made to correct the acidosis rapidly or fully. The use of sodium lactate (1/6 molar) to correct acidosis is not justified for two reasons: when sodium bicarbonate solution for injection is available (a) it depends upon the body oxidative mechanisms for conversion to bicarbonate; and (b) it can cause lactic acidosis.

Administration of excessive alkali in the presence of marked kidney damage may cause tetany and pulmonary edema. Acidosis associated with renal failure, therefore, may be better managed by peritoneal dialysis or by hemo-dialysis. Chronic renal acidosis responds to alkaline mixture containing sodium citrate and citric acid. Shohl's mixture which is commonly used contains 140 gm. of citric acid and 90 gm. of sodium citrate per litre of water. The adult dose is 50-100

ml. per day.

Respiratory acidosis is often a terminal event in patients with extensive lung damage or respiratory centre failure. In general, it is difficult to treat. Intravenous or oral sodium bicarbonate should be tried as an emergency measure. Treatment of respiratory infection, if present, use of bronchodilators and intermittent oxygen may help some of these cases.

ALKALOSIS

Alkalosis is defined as a reduction in the total *hydrion content* of the body. *Alkalemia* is a reduction in the *hydrion concentration* of the plasma, manifested as an increase in the blood pH. Alkalosis without alkalemia is called compensated alkalosis, that accompanied by alkalemia is called decompensated alkalosis.

(a) **Metabolic alkalosis:** Normally, in the presence of healthy kidneys an individual can tolerate large daily doses (140 g.) of sodium bicarbonate for about 3 weeks, without any gross disturbances. Alkali ingestion in the presence of renal damage, however, may cause alkalosis, as the renal excretion of bicarbonate is affected. Excessive vomiting or gastric suction can cause a marked loss of body hydrion and chloride, producing alkalosis. Excessive milk and alkali ingestion can also cause alkalosis of the 'milk-alkali syndrome', where high calcium content of the milk may probably aggravate the symptomatology. The blood pH and plasma bicarbonate show a rise. The urine is usually alkaline, containing excess of bicarbonate. In patients with severe electrolyte depletion, however, urine may be scanty and acidic; this is most probably due to accompanying potassium depletion which leads to increased renal tubular secretion of hydrion.

By itself, renal damage causes acidosis rather than alkalosis.

(b) **Contraction alkalosis:** This type of alkalosis was mainly seen following the administration of mercurial diuretics, which cause excessive loss of chloride and sodium; the bicarbonate loss

is smaller. Hence, the same amount of HCO_3 is distributed in a smaller volume of ECF. Since pCO_2 remains the same, the ratio of $\text{pCO}_2/\text{HCO}_3$ decreases. Such alkalosis caused mercurial resistance. Administration of ammonium chloride corrects the chloride loss.

(c) **Hypokalemic alkalosis:** This has already been discussed.

(d) **Respiratory alkalosis:** Excessive ventilation (hyperventilation) which washes away large amounts of carbon dioxide formed in metabolism, causes lowering of the arterial pCO_2 and reduction in the ratio $\text{H.HCO}_3/\text{B.HCO}_3$ with a fall in hydrion content. This is respiratory alkalosis, commonly seen following hyperventilation, involuntarily carried out by certain individuals probably in response to anxiety. Physiologically, it can occur at high altitudes during climbing. A similar phenomenon can occur in fevers, encephalitis, hypothalamic tumors, following drugs like salicylates, analeptics and even a hot bath.

Excessive washing out of potential hydrion would tend to raise the blood pH. This is initially countered by transfer of cation (B) from ECF to ICF, release of chloride into ECF by red cells and lactate from the muscles. This causes decrease in B and replacement of HCO_3 by chloride, resulting in correction of the $\text{H.HCO}_3/\text{B.HCO}_3$ ratio. Later, kidneys eliminate more cation and bicarbonate, the urine becoming alkaline. In contrast to metabolic alkalosis, the plasma bicarbonate is decreased. In later stages, the urine may become acidic, particularly in patients with marked depletion of sodium and potassium.

Clinical manifestations of alkalosis: In functional cases, respiratory alkalosis is episodic and is associated with feeling of tingling and muscle cramps; sometimes tetany can occur. Tetany in alkalosis is probably due to lowering of plasma ionized calcium and responds to intravenous administration of calcium gluconate; increased neuromuscular irritability due to raised blood pH also contributes to this phenomenon. Tetany following hyperventilation needs no

treatment other than reassurance and a demonstration to the patient about its mode of production. All attempts should be made to convince the patient about its harmless nature.

Chronic metabolic alkalosis causes anorexia, apathy and mental disturbances. Kidney function may be impaired and attacks of tetany can occur.

Treatment of alkalosis: This is aimed at removal of the cause and correction of the body fluid disturbances. Acute loss of chloride due to vomiting can be corrected by giving intravenous normal saline. In chronic cases, similar treatment given orally is adequate, except that occasionally an associated potassium loss needs to be rectified. A 0.9 per cent solution of ammonium chloride can be administered intravenously, but this is rarely necessary. Intravenous ammonium chloride may cause acidosis and ammonia poisoning; hence, 5 per cent arginine hydrochloride has been used. Alkalosis due to disturbances of respiratory centre is difficult to treat.

MANAGEMENT OF WATER AND ELECTROLYTE DISTURBANCES IN CHOLERA AND ACUTE DIARRHOEA

Cholera is still a fairly common disease in many tropical countries including India. Massive diarrhoea with watery stools, so characteristic of this condition results in a marked depletion of sodium, potassium and bicarbonate and in metabolic acidosis. Hence, replacement of the fluid and electrolyte losses forms the most important therapeutic aspect of this condition. It is of course ideal to tailor-make the fluid and electrolyte therapy in a seriously ill patient by monitoring the blood chemistry. This, however, is not always possible.

Principles of therapy:

(1) Correction of water loss, electrolyte loss and acidosis.

(2) Administration of antibiotics like tetracyclines and chloramphenicol. Usually, tetracy-

cline is administered orally in the dose of 500 mg. 6 hourly for 2 days, and then 250 mg. 6 hourly for further 3 days. Chloramphenicol can be used orally in similar doses.

(3) Treatment of complications such as shock and acute renal failure, which is discussed elsewhere.

(4) Supportive therapy such as intravenous glucose for giving nutrition, antidiarrhoeal compounds and oxygen, if necessary.

Management of dehydration: The extent of dehydration in cholera can be estimated by noting the quality of pulse, blood pressure, condition of the neck veins and skin turgor. The plasma protein concentration can be a reliable guide in judging the degree of dehydration. Plasma specific gravity can be measured by a simple method, using copper sulfate solutions of various specific gravities. Normal plasma specific gravity is 1.025. It has been estimated that for each 0.001 increase in the plasma specific gravity, an adult patient requires about 4 ml. per kg. body weight of fluid. The total fluid requirement can thus be estimated. In an emergency, isotonic saline along with isotonic sodium bicarbonate, should be used in the proportion of 2:1. This would correct sodium loss and acidosis. Potassium should be given, preferably orally. About 15 m. equiv. of potassium is needed to correct the potassium loss in a litre of stools. The quantity of stools passed should, therefore, be noted. The requisite quantity of potassium can be conveniently administered as 200 ml. of coconut water for each litre of stools passed. Alternatively, potassium salts such as potassium citrate and bicarbonate may be given orally or intravenously. If intravenous sodium bicarbonate is not available, 5 per cent solution of sodium bicarbonate may be given orally ad lib; this would correct the acidosis to some extent.

Coma and convulsions during diarrhoea often indicate hypoglycemia and i.v. glucose is needed.

The intravenous fluids are given rapidly initially, at the rate of at least 100 ml. per minute in a collapsed patient, to correct hypovolemia and to

avoid irreversible shock. Later on, the infusion may be adjusted according to the loss of fluids in stools and sweat. In practice, intravenous therapy is monitored by noting the state of the neck veins and the urine output. Usually intravenous fluid therapy is continued until the shock state is corrected and the patient is strong enough to drink the *oral glucose-electrolyte solution*.

In human cholera, water, sodium and chloride are not retained very much during oral administration of an isotonic electrolyte solution that does not contain glucose. It has, however, been demonstrated that the sodium and water absorption by the small bowel is very much enhanced by the addition of glucose to the oral fluid. Patients with dehydration can be successfully treated with oral fluids containing glucose, once the initial hypovolemia is corrected by 2-4 litres of intravenous fluid replacement. It has been shown that the moderate dehydration and severe acidosis due to cholera can be corrected in 3-6 hours by such oral therapy alone. This certainly has advantages where facilities for intravenous therapy are inadequate or not at all available. Patients strong enough to drink generally take the solution avidly. They may continue to vomit and in some cases the stool volume may increase. In spite of this, there is a net absorption of water and electrolytes. Moreover, vomiting which is probably caused by acidosis and volume depletion is likely to be corrected by the oral therapy itself. The solution need not be sterile and can be prepared on spot with components purchased from the local bazar. The oral treatment is far less expensive than intravenous fluids. No expertise is needed to administer the fluid by mouth. It can be given by family members and non-professionals as well as by health workers. A conscientious mother can work wonders. One teaspoonful given to a child every minute can provide 200-300 ml. per hour. Adults can take 750-1000 ml. per hour for several hours until signs of dehydration disappear and abundant pale urine is produced. If the patient needs rest, the same fluid may be given by a nasogastric tube.

The W.H.O. has recommended the fluid as shown in Table 33.3 for oral rehydration therapy (O.R.T.).

Table 33.3: Composition of Oral Rehydration Solution (O.R.S.)

Substance	Weight (g)	Home measure	Components (mMol/l)
Sodium chloride (Table salt)	3.5	1 teaspoon	Na ⁺ 90
Potassium chloride	1.5	½ teaspoon	K ⁺ 80
Sodium bicarbonate*	2.5	¾ teaspoon	HCO ₃ ⁻ 30
Glucose**	20	2 tablespoons	Glucose 110
Water	1000	1 litre	Water.

1. * Trisodium citrate dehydrate 2.9 g (3/4 teaspoon) which gives 30 mMol/L of citrate can replace sodium bicarbonate. Citrate in O.R.S. has been found to diminish stool output in high output diarrhoeas.

2.** Glucose 20 g can be replaced by 40 g of sucrose. Alternatively, it can be replaced by 50 g of cooked rice powder, which is more easily available and has the advantage of reducing both volume and duration of diarrhoea. The use of rice congee is traditional in India.

3. Addition of glycine 20 g also keeps to reduce the volume and duration of diarrhoea.

4. The constituents of the above fluids may be available in packets.

Proper institution of ORS therapy would avoid shock from continuing diarrhoea. The same type of fluid is also useful to treat the dehydration in other diarrhoeas. (see Chapter 37) Children under five years should be given plain water in addition to above solution in quantities approximately 1/3rd of the total volume administered.

The correct concentration of Na and glucose in the O.R.S. is critical for optimal effect and safety. The ORS administered cannot greatly exceed plasma in osmolality without the risk of increased diarrhoea and hypernatremia. Fortunately, nature has provided foods containing starches such as cereals and roots which have low osmolality in solution. Recent studies have indi-

cated that ORS in which rice and other food sources of starch are substituted for glucose effectively replace lost fluids, decrease vomiting, and reduce the severity and duration of diarrhoea.

Although glucose based ORS effectively replaces the fluids lost in the stool by patients with diarrhoea, it does not decrease and may slightly increase the stool volume. Secondly, glucose based ORS, if prepared with electrolyte concentration higher than the recommended ones, as a result of the addition of too much solute to a standard volume of water, can produce an increase in both diarrhoea and hypernatremia. Several studies have now shown that cereal based solutions are equally effective in reducing volume losses, can substantially reduce losses of intestinal fluid and may also shorten the duration of illness.

Physiologically, cereal-based ORS are identical to their glucose based counterparts. The dominant component in the cereals is starch from rice, corn, wheat, potato, sorghum, millet or even plantain. Starch is a large polymer of glucose that, on exposure to amylase in the intestine, is digested into smaller polymers that are then split by maltase into glucose at the intestinal brush border. This digestive process supplies a larger number of glucose molecules with which to transfer sodium ions from lumen into the blood, while generating less luminal osmotic "black drag" than would the direct ingestion of an equivalent amount of glucose. The cereal proteins also provide small peptides and amino acids which also facilitate the absorption of additional sodium ions. Of course, the presence of sufficient digestive enzyme is essential to the success of such solutions. In the vast majority, this is not the problem, but it may in infants under 4 months in whom intestinal glucoamylase is not fully developed. Addition of sodium bicarbonate and potassium chloride is not critical to success of cereal based ORS.

34 Nutritional Supplementation Therapy

Nutritional supplementation therapy is an important part of the total therapeutic planning, and without it, pharmacotherapy and surgery may not be optimally effective. In fact, there are diseases (e.g. phenylketonuria) in which nutritional therapy is the only treatment available. Complete coverage of nutritional therapy is, however, beyond the scope of this book. This chapter outlines the principles of nutritional supplementation in adults, mainly in acute medical and surgical illnesses.

NUTRITIONAL REQUIREMENTS IN HEALTHY ADULTS

1. **Energy:** The total daily requirement (TDR) for energy must be met every day. Ideally, energy intake equals energy requirement unless weight gain or weight loss is desired. The best way of assessing whether a person is in energy balance ($\text{Intake} - \text{Requirement} = 0$) is to weigh him daily. TDR can be calculated as the sum of basal metabolic rate, energy expenditure on physical activity and specific dynamic action.

Basal metabolic rate (B.M.R) is the energy requirement at rest and is related to the body surface area.

Basal energy requirement in persons above the age of 20 years can be calculated by Wilmore's formula.

$$\text{B.M.R. (KCal/M}^2\text{/day)} = 24 \times \left[37 - \frac{(\text{Age}-20)}{10} \right]$$

A more rough and ready formula is

$$\text{B.M.R. (KCal/day)} = 24 \times 0.9/\text{kg.}$$

Because the second formula does not include a term for age, it tends to overestimate the basal requirement in older people.

Energy expenditure on activity (E.E.A) values for different physical activities are available from textbooks of physiology.

Specific dynamic action (S.D.A.) refers to the additional calories required to metabolise and utilise the delivered foods. It is estimated at 10% of the sum of B.M.R. and E.E.A.

2. **Proteins:** Unlike with fats and carbohydrates, the body has very little mobilizable protein store. All the proteins in the body are either structural or functional. Repairs of damaged tissue and recovery from an illness are critically dependent on readily available protein. In the absence of external supply of protein, there occurs breakdown of endogenous protein and hence damage to tissues. Therefore, negative protein balance can be harmful even in the short run. The average protein requirement in adults is 0.6g/kg/day, out of which at least 25-30% should be animal protein including milk. Protein requirement is often stated in terms of nitrogen requirement, where 1 g of nitrogen = 6.25 g of protein.

3. **Water :** Water requirement in healthy adults is around 40 ml/kg/day. This will allow the excretion of about 1000 ml of urine. In hot and dry climates, upto 800 ml/day should be added, especially in summer, to offset the insensible losses.

4. **Minerals:** Table 34.1 gives the daily mineral requirements.

Various trace elements are also required e.g. zinc, iodine, chromium, copper and manganese.

5. **Vitamins:** Recommended daily allowances (R.D.A.) for vitamins are given in Table 70.2 (See Chapter 70). Those not mentioned in that table are: panthothenic acid 4-7 mg., biotin

100-400 µg and vitamin K 70-140 µg.

Table 34.1 : Daily requirement of minerals

Mineral	Daily requirement
Sodium	1.4 - 2.0 m Eq/kg
Potassium	1.2 - 1.5 m Eq/kg
Calcium	0.2 - 0.3 m Eq/kg
Magnesium	0.3 - 0.45 mm Eq/kg
Iron	10 - 20 mg/day
Phosphorus	7 - 9 m Mol or 14-18 m Eq/1000 KCal/day.

6. **Essential fatty acids (E.F.A):** The R.D.A. for linoleic acid is 2-4% and that for linolenic acid 0.5% of the total daily calorie intake. The polyunsaturated fatty acid (linoleic + linolenic) content of the commonly used edible fats is as follows (all figures are in g per tablespoonful) : safflower oil 10, soyabean oil 7.4, cottonseed oil 6.8, maize (corn) oil 6.1, til oil 5.7, rice bran oil 4.7, groundnut oil 3.9, mustard oil 3.4, olive oil 1.35, palm oil 1.2, vanaspati 0.8, ghee 0.55 and coconut oil 0.3. Weekly ingestion of 50-100 ml of safflower oil, soyabean oil, cotton seed oil or corn oil satisfies the requirement for F.F.A.

ALTERATIONS IN NUTRITIONAL REQUIREMENTS IN ACUTE ILLNESS

1. Energy

(a) *Fasting and undernutrition* decrease the B.M.R. by about 25%.

(b) *Fever* increases the B.M.R. by about 13% for every degree rise of body temperature above 37°C. *Rigors* raise the B.M.R. further. Secretion of catecholamines in acute stress also elevates B.M.R. On the other hand, these conditions reduce the appetite and food intake (and hence S.D.A.), as well as physical activity (and hence E.E.A.).

(c) *Illness* : In addition to fever and its consequences, the hormonal response of the body to physical trauma and infection, as well as losses from the body (e.g. protein in burns), increase the

T.D.R. In illness, the calculations of energy requirement are based on B.M.R.; EEA and SDA are ignored for reasons already mentioned. Thus, in mild illness (elective hospitalization or mild infection) T.D.R.=110% of B.M.R.; in moderate illness (fracture or severe infection) T.D.R.=125% of B.M.R.; and in severe illness (severe burns or a combination of stresses) T.D.R.=150 to 200% of B.M.R. Thus, T.D.R. does not exceed twice the B.M.R. even in the most severe illness.

2. **Protein:** During acute illness, the protein requirements rise: 0.6-0.8g of protein/kg/day in mild illness, 0.8-1.0g/kg/day in moderate illness and 1-1.5g/kg/day in severe illness. For optimum utilization of protein, about 150 total KCal must be supplied per day per 6.25 g of protein or 1.0 g of nitrogen.

3. **Water:** The water requirement increases because of insensible sweating, visible sweating, vomiting, diarrhoea, burns or fistulae. At the same time, the intake is likely to be poor because of apathy, obtundation of consciousness, or damage to the thirst centre as in head injury. Electrolyte-free water (as 5% dextrose in water) must be made available to the patient parenterally under these circumstances.

4. **Electrolytes:** Their requirements go up if there are excessive losses from the body such as sweating, diuresis, vomiting, diarrhoea, aspiration or fistulae. They must be calculated and must be made good.

Iron requirements must be considered carefully in the presence of trauma and bleeding. Further, some patients may be anemic to begin with.

5. **Vitamins:** During acute illness, especially if it is prolonged, the requirements for vitamins go up because of the catabolic state. If the patient is unable to ingest a normal diet, water soluble vitamins should be supplemented daily and fat soluble vitamins once a week.

SEQUELAE OF MALNUTRITION

Malnutrition has several deleterious effects

which may impair patient's ability to recover from an acute illness.

- (a) Weight loss: Reduction in body fat and in muscle mass, and weakness.
- (b) Hypoproteinemia and edema.
- (c) Impairment of cellular and humoral immunity.
- (d) Delayed wound healing.
- (e) Deficiencies of vitamins and minerals.
- (f) Deficiency of E.F.A.: This is known to arise during the course of prolonged total parenteral nutrition. The deficiency causes dry, scaly cracked skin, coarse hair, hair loss, and may impair wound healing.
- (g) Malaise and poor morale.
- (h) Increased mortality.

ASSESSMENT OF NUTRITIONAL STATUS

A detailed history and physical examination, together with selected laboratory tests, help in the nutritional assessment of the patient. Deficiencies are commonly multiple; evidence of one deficiency should make one look carefully for other deficiencies. A nutritional assessment helps in estimating the overall nutritional impact of the disease; it helps to decide whether intensive nutritional support is necessary and if so how urgently; lastly, it helps to predict organ dysfunction which may dictate that elective surgery should be postponed.

Table 34.2 gives a protocol for assessment for protein-calorie status. Laboratory estimations of haemoglobin and of serum Na, K, Ca, P and Mg are other helpful parameters.

NUTRITIONAL SUPPLEMENTATION: AIMS AND INDICATIONS

Nutritional supplementation therapy aims at establishing or maintaining good nutritional status; establishing positive nitrogen balance and increasing weight in the malnourished; and overcoming the effects of malnutrition.

Nutritional intervention to prevent malnutrition or to replenish the malnourished patient im-

Table 34.2 : Assessment for Protein-Calorie Status

Parameter	Result which suggests significant malnutrition
Weight loss in adults *	
% loss in past 1 month	> 5
% loss in past 6 months	> 10
Serum albumin	< 2.8 g%
Serum transferrin from T.I.B.C. **	< 150 mg%
Total lymphocyte count	< 1200/cumm.

(Modified from Alpers, Manual of Nutritional Therapeutics, 1983, Little Brown and Company, Boston).

* It is necessary to distinguish between weight loss due to dehydration and that due to loss of fat or muscle.

** Transferrin (mg %) = $(0.83 \times \text{T.I.B.C.}) - 43$ where T.I.B.C. is the total iron binding capacity.

proves recovery and increases survival from many diseases.

Nutritional supplementation is indicated

1. to correct existing malnutrition;
2. to prevent malnutrition that will occur unless there is intervention (e.g. in patients in coma; in those with severe burns, serious intestinal obstruction, trauma or sepsis);
3. when bowel rest is required (as in acute symptomatic inflammatory bowel disease, acute pancreatitis, intestinal fistulae);
4. when serious G.I. symptoms occur during cancer chemotherapy or radiotherapy;
5. when mechanical problems exist (e.g. dysphagia, surgery of head or neck; and
6. after massive bowel resection or other disorders causing malabsorption.

ENTERAL NUTRITION

Nutritional supplementation may be done orally, by enteral tube feeding (forced enteral feeding, or parenterally; in the last case, it may be partial or total (Total Parenteral Nutrition, T.P.N.). Wherever possible oral and enteral tube feeding are the preferred methods.

Merits and disadvantages of feeding via the G.I. Tract:

The oral and enteral tube feeding use a

physiological route, are safe and inexpensive, and can provide almost any nutrient that is required. Further, luminal nutrition maintains the structural and functional capacity of the small intestine. Lastly, they are the methods of choice, whenever possible, if supplementation is going to last for more than a week. Calorie supplementation can be done easily and completely by these methods.

Oral supplementation requires satisfactory appetite, intact deglutition and the conscious co-operation of a patient; it also requires that the oral supplements must be palatable; it has no disadvantages.

Enteral tube feeding circumvents the need for adequate appetite and deglutition; it requires less cooperation from the patient and can be carried out even in an unconscious patient. Its disadvantages are (a) less acceptability than oral feeds; (b) nasopharyngeal irritation by the tube; (c) erosion of the esophagus; (d) infection of the nose, paranasal sinuses and ears; and (e) incompetence of the gastroesophageal sphincter with regurgitation of gastric contents into the esophagus followed by their aspiration into the tracheobronchial tree. To prevent the risk of regurgitation of gastric contents and pulmonary aspiration, the patient should be kept in a semi-sitting position (head of the bed elevated 30°) during feeding and for one hour thereafter. A 30° angle should be maintained for the elderly, infants and comatose patients. Enteral tube feeding should be done cautiously in patients with loss of gag reflex, hiccuping, a tendency to vomit or significant pulmonary dysfunction; under these circumstances bolus feeds and feeding by the nasogastric tube should be avoided; slow drip feeding by a nasoduodenal tube may be done with great caution.

Techniques of enteral feeding :

Oral supplementation with high calorie, high protein 'table foods' (milk; milk products such as cheese and ghee; meat; and groundnuts) is the most pleasant form of supplementation in

patients who can tolerate it and will cooperate in consuming them. Vegetables, fruits, fruit juices, dal, cereals and a multivitamin capsule would complete the list. Medium chain triglyceride (MCT) preparations (Precision LR, Pregestimil) containing 8-10 carbon, fatty acid residues are valuable in patients with steatorrhoea; these medium chain fatty acids are absorbed directly into the portal circulation without the help of bile salts. MCT preparations are however expensive.

The oral route can also be used to supplement the intake of water and electrolytes.

Enteral tube feeding can be carried out either by nasogastric or by nasoduodenal route in patients with intact G.I. tract, who are unconscious or who are not sufficiently cooperative to take all the calculated daily requirement by mouth. Local irritation and erosion can be minimised by using a small diameter tube, preferably made of plastic. Larger diameter tubes, however, permit the administration of an almost normal meal, blenderized to the consistency of a thick soup.

A problem with nasogastric feeding is the gastric distension, especially when bolus feeds are used. The nasoduodenal tube is more difficult to position properly, and diarrhoea is more likely to occur with nasoduodenal feeding; however, the problem of gastroesophageal reflux and its consequences are less troublesome. The other problems with enteral tube feeding are: electrolyte disturbances, volume overload, lactose intolerance, diarrhoea and hyperosmolality syndrome. They can be minimized by (a) proper adjustment of the composition of the feeds; (b) not using too much of milk but using buttermilk, instead; and (c) not being overambitious with tube feeding.

Bolus feeding : This is used only with nasoduodenal tube. Begin with 50-100 ml of a half strength feed every 3-6 hours; aspirate the gastric contents before each feed; flush the tube with water after each feed, and gradually increase the volume of a feed to 250-300 ml to be given every 3-4 hours. Finally, increase the concentration of the feed gradually to the full strength.

Continuous infusion : This can be employed with either nasogastric or nasoduodenal tube. The initial rate of 25 - 50 ml per hour is gradually increased, once in 24 hours, to 100 - 150 ml per hour. Additional water may be given to prevent hyperosmolality. A variety of foods can be used by this route: soups; fruit juice; milk, buttermilk, eggnog; blenderized normal meals (rice, chapatti, dal, vegetables, meat etc.); commercially available protein powders (Casilan, Protinex, Protinules, Trophox etc.).

Strict intake output charts must be maintained in patients on enteral tube feeding. Unfortunately, the enteral route is not available in patients with medical or surgical abdominal diseases.

PARENTERAL NUTRITION

Partial parenteral supplementation: Maintenance therapy with water and electrolytes is indicated in a patient who is temporarily unable to ingest food and fluids normally e.g. a postoperative patient. No pre-existing deficit or excess of water or electrolytes or altered renal function should be present. Such therapy should not be extended beyond 7 days, if it can be avoided. The daily maintenance requirement in an adult can be provided by 1000 ml of 0.9% NaCl in 5% dextrose in water (=170 calories); 1000 ml of 5% dextrose in water with 20 mEq of KCl added; and 1000 ml of 5% dextrose in water. It is customary to avoid infusing NaCl solution for 24 - 48 hours after surgery as the stress of surgery produces intense salt and water retention during this period. It must be remembered that even healthy postoperative patients tend to have glucose intolerance and can develop hyperglycemia even while receiving 5% dextrose in water. Water soluble vitamins should be given daily; remember to give enough thiamine as prolonged parenteral glucose supplementation without thiamine can precipitate acute thiamine deficiency and Wernicke's encephalopathy. Fat soluble vitamins should be administered once a

week. Calcium, magnesium, phosphorus and protein supplements become necessary if parenteral supplementation is continued beyond 1 week. Strict intake output chart should be maintained in these patients. Table 34.3 shows the composition of some fluids for intravenous use. All these solutions can be administered through a peripheral vein. Table 34.4 shows the composition of some parenteral additives.

Table 34.3 : Composition of some fluids for intravenous use

Solution	Dextrose (g/L)	Na (mEq/l)
5% dextrose in water	50	-
5% dextrose in saline	50	145
0.85% (isotonic) saline	-	145
0.9% saline	-	154
Ringer lactate*	-	130
5% saline	-	855
1/6th molar lactate	-	167

* Also contains potassium 4 mEq/l, chloride 109 mEq/l (as against 154 mEq/l of 0.9% saline), calcium 3 mEq/l and lactate 28 mEq/l.

Table 34.4 : Composition of some parenteral additives

Solution	Volume per ampoule	Cation (mEq/ampoule)	Anion (mEq/ampoule)
7.5% sodium bicarbonate	50 ml	44.6	44.6
15% potassium chloride	30 ml	60.0	60.0
10% calcium gluconate	10 ml	4.6	4.6
50% magnesium sulfate (MgSO ₄ · 7H ₂ O)	10 ml	40.6	40.6
42% disodium hydrogen phosphate (Na ₂ HPO ₄ · 12 H ₂ O)	15 ml	36.0	36.0*
46% potassium dihydrogen phosphate (KH ₂ PO ₄)	15 ml	100.00	100.00**

* equal to 18 mMol ** equal to 50 mMol.

Phlebitis is a well recognized complication of intravenous infusion therapy. Such phlebitis may be either infective or noninfective. Contamination of the fluid to be infused during

manufacturing process, frequent manipulations of the intravenous system, and entry of bacteria at the cannula-skin junction, all account for the infective phlebitis. However, most phlebitis following intravenous infusions is non-infective. Many factors contribute to it; they all seem to operate through mechanical and physicochemical interaction at the cannula-vein junction. These factors are (1) the type of cannula: metal cannulae cause less phlebitis than plastic ones and short cannulae less than long ones; (2) duration of cannulation: the longer the cannulation, the greater the risk of phlebitis; (3) the location of the cannula: veins in the upper extremity and the large central veins are less liable to develop phlebitis than those in the lower extremity and the periphery; (4) the type and composition of the infusate and the presence of additives in it. Certain drugs are more liable to produce phlebitis than others. Fluids with non-physiologic pH, hypertonic fluids and fluids which contain particulate matter are prone to produce phlebitis. Particulate matter is often present in solutions that appear clear to the naked eye, and comprises glass, cotton fibres, precipitated proteins, microcrystalline drug particles, and degradation products of interaction between fluids and glass, plastic or even rubber stoppers. The above list of causes of phlebitis suggests possible ways of preventing it. Catheter sepsis can be a serious complication during prolonged intravenous infusion therapy. It can be prevented by (a) insertion of the catheter under aseptic conditions; (b) subcutaneous tunneling of the catheter; (c) use of transparent polyurethane dressings over the side of cannulation; (d) changing of dressings by experienced staff; (e) change of the infusion set every 2-3 days; and (f) administration of blood products or drugs via separate set from the one used for the main infusate. Finally, catheter sepsis should be the uppermost in the physician's mind when a patient receiving an intravenous infusion develops fever or any metabolic deterioration. A special in-line filter in the infusion line has been developed to intercept any particu-

late matter in the fluid; it is under evaluation.

TOTAL PARENTERAL NUTRITION (TPN)

TPN is used to supply all the essential nutrients without using the gastrointestinal tract.

Indications for TPN: TPN has been documented to be valuable in (1) short bowel syndrome; (2) prolonged ileus, such as that following visceral trauma; (3) pancreatic abscess/fistula; (4) intestinal fistula; (5) hypermetabolic states, such as severe burns, major sepsis; (6) alimentary tract cancer causing mechanical obstruction; (7) severe vomiting or anorexia, such as anorexia nervosa, hyperemesis gravidarum; and (8) Crohn's disease with malabsorption and retarded growth in children.

It has also been used in other situations such as for routine preoperative support and as an adjunct to cancer chemo-/radiotherapy; its usefulness in these circumstances is not proven.

TPN has been used in the hospital setting as well as at home. It has been shown to achieve positive nitrogen balance, and to promote growth in children. One of the aims of TPN is to ensure complete bowel rest which minimises the intestinal motor and secretory activity and encourages the healing of bowel lesions.

Composition and requirements:

Calories : These are provided by means of 20 - 25% dextrose in water through a central vein, as it is hypertonic. **Water** is provided in the quantity of 40ml/kg/day.

Protein : This is supplied in the form of specially prepared mixtures (Hermin, Astymin-3) of synthetic, essential amino acids. They contain 8 - 9% of the amino acids in 200 ml bottles for intravenous use. The calories provided by the amino acids are not taken into account in the daily calorie calculation. These mixtures are used as a source of protein as the endogenous protein breakdown is less when some protein is made available than when only carbohydrate is

supplied. Further, the protein prevents fatty infiltration of the liver which is likely to occur when only carbohydrate is supplied to the patient. Patients who are losing protein in exudates need infusion of human serum albumin in the dose of 10-25 g/day; they and anemic patients also benefit from blood transfusions. Amino acid mixtures and albumin solutions, however, are expensive.

Fats : Milky emulsions of soyabean oil (Intralipid 10% and 20%) and safflower oil (Liposyn 10% and 20%) in combination with glycerol and emulsifying agents are available for intravenous administration. The 10% emulsions supply 1.1 calorie per ml. Both are good sources of linoleic acid; the soyabean oil preparations are a good source of linolenic acid as well. Fat emulsions are not commonly used daily as a source of calories, as they are expensive. A weekly injection of 500-1000 ml of a 10% emulsion is used to provide the necessary essential fatty acids to prevent the development of a deficiency syndrome. As the fat emulsions are isotonic, they can be administered by a peripheral vein.

Minerals : Mineral requirements are as per Table 34.1. In addition, trace elements are supplied as follows: Zinc 2.5-4 mg/day; copper 0.5-1.5 mg/day; iodine 75-150 µg/day; manganese 0.15-0.8 mg/day; chromium 10-15 µg/day; and selenium 50-200 µg/day. They are added to the intravenous infusion.

Vitamins : A multivitamin preparation (B group with Vitamin C) is given daily in the amino acid/glucose solution. A second preparation containing the fat soluble vitamin is given once a week. The weekly intake of vitamin D by this route should be limited to 200 I.U., as prolonged use of large doses has been shown to cause a reversible, metabolic bone disease. The recommended amounts of vitamin supplements during TPN are as follows: (a) daily: thiamine 3 mg, riboflavin 3.6 mg, pantothenic acid 15 mg, pyridoxine 4 mg, niacin 40 mg, biotin 60 mg, folacin 400 µg, cyanocobalamin 5 µg, and ascorbic acid 100 mg; (b) weekly: vitamin A 3300 I.U., vitamin D 200 I.U. and vitamin E 10 I.U.

Technique of TPN : The base solution for TPN is a mixture of an amino acid solution and dextrose solution (final concentration of dextrose 20-25%); it is prepared daily by mixing an amino acid solution and a dextrose solution in a laminar flow hood in the hospital pharmacy. The minerals and vitamins are added to this base solution. The calorie content of dextrose solution is calculated on the basis of 3.4 KCal per gramme as the dextrose used is not anhydrous (=4 KCal/g) but in the form of monohydrate. The calorie contribution of amino acids is ignored. The total calories supplied should bear a ratio of 125-190:1 to nitrogen (in g) supplied, in order to optimise the utilization of the amino acids for anabolic purposes. *As the base solution is hypertonic, it must be infused through a central vein, taking all the precautions detailed above.* The lipid emulsion is administered separately through a peripheral vein.

In order to prevent cracking, nothing should be added to the fat emulsion.

Insulin (soluble) in the dose of 10 units per 250 g of dextrose is added to the base solution to prevent hyperglycemia. **Heparin** may be added to the infusate to prevent fibrin plugging of the central venous catheter. If corticosteroids are required for the patient's primary condition, they (preferably those with little mineralocorticoid activity, such as dexamethasone) may be added to the base solution.

TPN is generally initiated with one litre of the base solution (containing about 250 g of dextrose and about 40 g of amino acids) per 24 hours. If this amount is tolerated, the quantity infused is increased by -1 litre per day till the desired amount of calories and protein are being delivered. This concentrated glucose solution is infused in 18 hours and 5% dextrose infused during the remaining 6 hours of the day; this helps to prevent rebound hypoglycemia. Further, when TPN is being discontinued, the amount of glucose infused should be tapered gradually for the same reason.

Physical therapy is a valuable adjunct for

restoring muscle function and muscle mass in patients on TPN.

Monitoring of TPN : Patients on TPN need close clinical and laboratory monitoring. A strict intake output chart must be maintained. The daily physical examination of the patient should include weighing, looking for signs of fluid overload and for TPN related sepsis. Daily examination of urine for glucose and acetone, and daily estimation of plasma glucose, urea nitrogen, creatinine, Na, K, Ca, Mg and P should be done till the patient stabilizes. The appearance of hyperglycemia during apparently stable TPN suggests a catabolic stress such as catheter sepsis. Serum bilirubin and liver enzymes should be done once in 3-4 days to detect hepatic dysfunction.

A weekly weight gain of about 1.5 kg indicates successful TPN. Improvement in muscle strength is a good indication of improved skeletal muscle function. Anthropometric measurements of muscle mass are not expected to change during an average hospital course of TPN. Improvement in plasma albumin and transferrin occurs only

gradually. Growth is known to be normalised in children with retarded growth due to inflammatory bowel disease and malabsorption.

Complications of TPN: A variety of complications can occur in a patient on TPN. An attempt should be made to prevent them; at the same time they should be carefully looked for and treated promptly and vigorously, if they occur. The complications are: (1) hyperglycemia; (2) rebound hypoglycemia on cessation of TPN; (3) electrolyte abnormalities; (4) azotemia; (5) liver dysfunction; (6) volume overload; (7) metabolic bone disease; and (8) a variety of non-metabolic complications such as adverse reactions to lipid emulsion; sepsis; allergic reactions; and complications due to the physical trauma by the catheter in the vein.

TPN is more expensive, and requires more careful monitoring than enteral nutrition. Therefore, it should not be instituted unless it is absolutely necessary. Further, an attempt should be made to re-establish enteral supplementation as soon as possible in all patients who are treated with TPN.

35 Diuretic and Anti-Diuretic Drugs

The kidney is not just a simple excretory organ but it plays an important role in regulating the volume and the composition of the body fluids. The functional unit of the kidney is termed as the nephron. Drugs can modify the renal functions either indirectly by modifying its circulation or directly by affecting the nephron function. Most of the therapeutically useful agents act mainly by modifying various functions of the nephron.

Physiology of urine formation: The volume and composition of urine are essentially determined by (1) glomerular filtration, (2) tubular reabsorption and (3) active tubular secretion. Diagrammatic representation of a nephron is shown in Fig. 35.1.

Urine formation begins in the glomerular capillary tufts by the process of ultra filtration. The composition and the volume of fluid filtered out from the plasma depend upon the composition of the plasma, the condition of the glomeruli and the blood pressure within them. The glomerular filtrate is a protein-free ultra filtrate

of the plasma. The glomerular filtration rate (GFR) can be measured by using a substance like inulin (inulin clearance) which, when injected is filtered by the glomeruli and does not undergo either reabsorption or secretion by the renal tubules. The renal plasma flow can be estimated by measuring the clearance of a substance like para-amino-hippuric acid, which is completely cleared by the kidney in one single passage of blood by combined glomerular filtration and tubular secretion. Both the renal plasma flow and glomerular filtration can be affected by various factors which may cause sodium retention and edema; important among these are cardiac failure, renal vascular disease and certain vasoconstrictor drugs like noradrenaline. Xanthine derivatives like theophylline increase the renal blood flow. The G.F.R. is directly related to the cortical blood flow. 90-95% of the renal blood flow passes through the cortex. The medullary blood flow does not contribute significantly to G.F.R. but is of importance in the concentrating

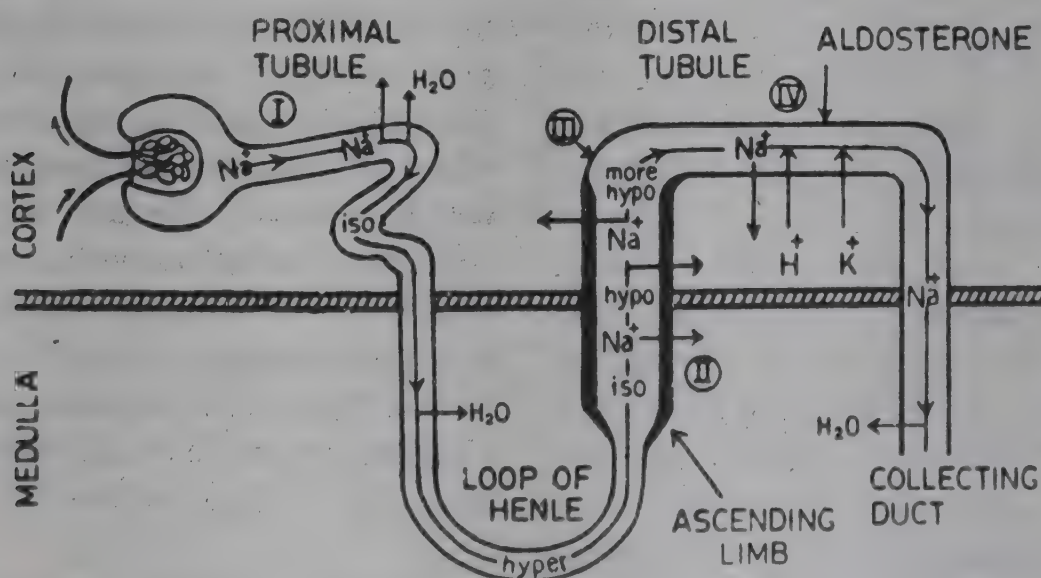


Fig. 35.1 : The simplified schematic diagram showing functional subdivisions of a mammalian nephron and sites of diuretic action on sodium reabsorption--(I) Proximal tubule, (II) Ascending limb of Henle's loop, (III) Early distal tubule and (IV) Distal tubular Na/K exchange site.

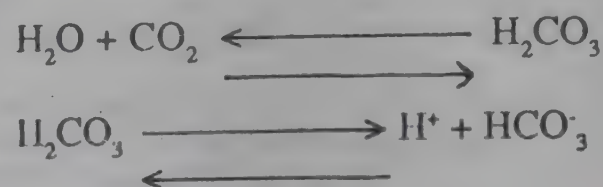
ability of the kidney. The medullary blood flow is highest during maximum diuresis and is reduced during maximum anti-diuresis. The mechanism by which the tubule reabsorbs various substances is not well understood. Nearly 80 per cent of the filtered sodium, most of the potassium, amino acids and glucose are reabsorbed in the proximal tubule, by active processes. Proportionate quantities of water are also absorbed along with sodium (obligatory reabsorption), so that the fluid within the tubular lumen remains isotonic with plasma. Reabsorption of sodium in the proximal tubule varies with changes in E.C.F. and in G.F.R.; sodium reabsorption at this site is enhanced markedly in response to contraction of E.C.F. volume and acute reduction in G.F.R. from any cause. It has been suggested that expansion of E.C.F. volume causes the release of a natriuretic hormone which depresses sodium reabsorption at this site. Reabsorption of sodium establishes an electrochemical gradient which determines the reabsorption of chloride. This then establishes an osmotic gradient along which water is reabsorbed. Removal of water from the tubular lumen sets up a concentration gradient for urea which is then reabsorbed. Thus, reabsorption of sodium is probably the event of primary importance in tubular reabsorption.

Quantitatively less sodium is absorbed from the next portion of the nephron, namely the loop of Henle. The loop, however, is of considerable interest since it is believed to act as a counter-current multiplier. According to the counter-current concept, the descending and the ascending limbs of the loop have relatively different permeabilities to water and sodium. Hence, sodium along with the anion is reabsorbed from the ascending limb without accompanying free absorption of water, resulting in the delivery of hypotonic fluid to the distal convoluted tubule (Site IV, Fig. 35.1). This also results in an increase in the solute concentration and consequent increase in the osmotic pressure in the renal medullary region. In the descending limb, water diffuses out into the hypertonic surroundings and

sodium enters the tubular lumen from the latter. Hence, the tubular fluid, which is isotonic with plasma at its entry into the descending limb of the loop of Henle, becomes progressively more hypertonic as it approaches the tip of the loop. From then on, its osmolality diminishes progressively because of active extrusion of chloride (accompanied by sodium) from the ascending limb of the loop, till the fluid entering the distal convoluted tubule is hypotonic to plasma. This circular and repetitive transfer of sodium (ascending limb \rightarrow interstitium \rightarrow descending limb \rightarrow ascending limb and so on) is called the 'hairpin counter-current multiplier system'. It is largely responsible for creating a hypertonic medullary interstitium and thus for the concentrating ability of the kidney. The mechanism by which such transport of sodium takes place in the loop is not known. However, preferential transport of sodium by the ascending limb of Henle's loop with its low water permeability is believed to be important in the process of concentration of the urine by the mammalian kidney.

The active reabsorption of sodium along with the anions continues in the distal convoluted tubule. In addition, it is at this site that an exchange of sodium for potassium and hydrogen ions occurs. Most of the potassium filtered by the glomeruli is reabsorbed in the proximal tubules and the fluid presented to the distal tubule probably does not contain any potassium. The potassium that appears in the urine is, therefore, secreted by the distal tubule in exchange of sodium which is reabsorbed. The exchange of potassium with sodium in the distal tubule is largely but not completely under the influence of aldosterone, excess of which causes sodium retention and potassium depletion.

The tubular cells contain an enzyme known as carbonic anhydrase which helps to form carbonic acid in the cells as follows:



The hydrogen ion derived from the carbonic acid is exchanged with sodium from the tubular lumen which combines with bicarbonate in the tubular cell and returns to ECF as sodium bicarbonate. This is how the body conserves the base. Addition of H^+ ion to the tubular fluid makes the normal urine acidic. The presence of bicarbonate and phosphate buffers in the filtrate prevents the tubular fluid from becoming excessively acidic. Renal tubular cells also produce ammonia (NH_3) which diffuses and reacts with hydrogen ion in the urine to form NH_4^+ which cannot be reabsorbed. The acidification of urinary buffers and formation of ammonium ion are thus necessary for the reabsorption of sodium bicarbonate.

The final volume and composition of the urine to be excreted are regulated by the collecting duct which runs from the relatively iso-osmotic cortex through the hyperosmotic renal medulla to the papilla. The urine entering the collecting tubule is isotonic with plasma. Under the influence of ADH, collecting ducts are relatively permeable to water which passes freely to hyperosmotic renal medulla, thus concentrating the urine further. This, however, does not occur in the absence of ADH. In addition, collecting ducts have been shown to reabsorb sodium actively and to secrete hydrogen and ammonium ions.

Since tubules normally absorb over 99 per cent of the glomerular filtrate, marked diuresis can be achieved by interfering with the tubular reabsorption of sodium. The distal convoluted tubule, the collecting duct and the ascending limb of the loop of Henle have reserve capacity for reabsorption of sodium. This may be utilized when sodium reabsorption is decreased in the proximal tubule. Hence, a diuretic agent acting on the proximal tubule alone may not necessarily cause increased sodium excretion since its effect will be counterbalanced by increased distal reabsorption.

DIURETICS

Drugs which increase the rate of urine forma-

tion are called diuretics.

Experimental evaluation of diuretics: Experimentally, drugs are tested for potential diuretic properties in rats or dogs. Animals used are hydrated by giving water equal to 5 per cent of body weight, to ensure continuous diuresis. Urinary output is measured at 5 and 24 hours after drug administration along with the estimation of its sodium, potassium, bicarbonate, and titratable acidity content. The results are compared with similar values in the controls. Un-anaesthetised trained female dogs are also used for similar diuretic studies.

Although a good deal of information can be obtained from animal studies, these cannot be directly applied to man. Ethacrynic acid, a potent diuretic in man, has no diuretic or saluretic action in rats. Further, there is no appropriate animal model comparable to the edematous state in patients. Hence, every new diuretic drug has to undergo experimental evaluation in man. Such studies are usually carried out both in normal human subjects and in edematous patients.

In case of normal volunteers, the intake of sodium and fluid in the diet is regulated, although rigid control of quantity is not needed. Excessive activity is avoided during the studies since it is known to affect body electrolyte and fluid homeostasis. First, the control patterns of electrolyte and fluid balance under standardized conditions are studied in each individual and then the dose response relationship for the new diuretic compound is determined. Usually, several parameters such as weight loss, urinary volume and output of Na^+ , K^+ , Cl^- and HCO_3^- are studied. Such studies provide information about the potency of the compound, its range of application and the maximum effective dose in man. In order to evaluate the comparative efficacy, it is necessary to determine the maximally effective dose or 'ceiling dose' of the new compound.

Evaluation of a diuretic in edematous patients, though undoubtedly important, presents many difficulties. The subject material is variable both in respect to etiology and severity of the disease.

Activity and presence of complications such as infection and cardiac arrhythmia may distort the drug effect. Mere bed rest and treatment of infection can produce substantial diuresis in congestive cardiac failure. Under such circumstances, interpretation of the drug response may be erroneous. Even a change in posture can affect the diuretic response to a drug, horizontal position enhancing its action. Lastly, the diuretic response in edematous patient varies according to the severity of edema and alterations in renal function.

Various methods have been employed for clinical assay of diuretic activity of various drugs in edematous patients. The commonly employed procedure is one suggested by Gold and his associates which involves the administration of 'ceiling doses' of test and standard diuretic compounds to the same patient, given in an alternating sequence; each sequence of four spaced doses provides data for two paired comparisons between the drugs under investigation. Various modifications of this method are now available.

Classification of diuretics: Only a few drugs produce diuresis by increasing the filtration rate at the glomeruli, and these are relatively weak in action. Most of the diuretics used therapeutically act by interfering with sodium reabsorption by the tubules. The exact mechanism of action of all these drugs at the cellular level is unknown.

Diuretics can be classified therapeutically into weak, moderately potent, very potent and potassium sparing diuretics.

I. Weak diuretics:

(a) Osmotic diuretics:

(i) *Electrolytes* e.g. sodium and potassium salts.

(ii) *Nonelectrolytes* e.g. mannitol, isosorbide, sucrose, and glycerol.

(b) Acidifying salts such as ammonium chloride and arginine hydrochloride.

(c) Xanthine derivatives e.g. aminophylline.

(d) Carbonic anhydrase inhibitor e.g. acetazolamide.

II. Moderately potent diuretics e.g. benzothiadiazine compounds, chlorthalidone, chloroxolone and clopamide. These drugs have a moderately rapid onset of action, lead to excretion of 5-10% of the filtered NaCl and have a wide spectrum of duration of action (8-72 hours). They are ineffective with G.F.R. below 20 ml/minute.

III. Very potent diuretics (High ceiling diuretics) e.g. parenteral organic mercurial compounds, furosemide, mefruside, bumetamide and ethacrynic acid. These drugs have a rapid onset and short duration of action. The nonmercurials among this group are often called '*loop diuretics*' as their chief site of action is the loop of Henle. They cause excretion of 15-20% of the filtered NaCl and tend to be effective when drugs from group II, given in maximum doses, fail to act in a given patient. They are effective even in the presence of markedly reduced G.F.R.

IV. Potassium sparing diuretics e.g. triamterene, amiloride and the aldosterone antagonist spironolactone. By themselves, they are weak diuretics and cause excretion of less than 5% of the filtered NaCl. They are, however, useful adjuncts to the drugs from group II and III because of their potassium sparing effect.

Water, given in excess, can act as a physiological diuretic. During water diuresis the influence of ADH remains inhibited and the ADH responsive portion of the nephron becomes impermeable to water. The urine excreted consists of water that is excreted along with the electrolytes (osmolar clearance) as well as the solute free portion (free water clearance). In water diuresis, water is removed from the body greatly in excess of the solute. It will thus increase the osmolality of body fluid. For the mechanism of water diuresis see later. In edema, the basic problem is sodium retention, the water retention being secondary. In such cases, water does not act as a good diuretic. Conversely, in patients with sodium retention, there need not be a rigid restriction of water intake when sodium intake is restricted. Water diuresis is recommended to wash out

certain drugs which irritate the urinary tract or are of limited solubility in the urine, such as salicylates or sulfonamides. It helps to increase the clearance of substances like urea and various drug metabolites. It is also useful in urinary tract infections.

OSMOTIC DIURETICS

Osmotic diuretics are solutes which have the following properties: (1) they are pharmacologically inert; (2) they are (generally) non-metabolizable; (3) they are freely filtered at the glomerulus; and (4) they are not significantly absorbed by the renal tubules.

In the proximal tubule, sodium is actively absorbed from tubular lumen, dragging water passively along with it. In the presence of a non-absorbable solute (e.g. mannitol), diffusion of water is reduced relative to that of sodium. As a consequence the net absorption of sodium diminishes. There is an enhanced urine flow with a relatively smaller increase in the excretion of sodium salts. The other osmotically active solutes that produce this effect are urea, glucose, isosorbide, and urographic and angiographic contrast agents. In case of glucose, this mechanism becomes operative when the tubular maximum for reabsorption of glucose is exceeded because of hyperglycemia.

When GFR is acutely reduced (as in hypotension or dehydration), solutes undergo more complete reabsorption in the proximal tubule, so that there is a marked fall in the urine flow and solute excretion. Administration of a normal solute such as sodium chloride under these circumstances is unable to induce diuresis because of the near complete reabsorption of sodium as long as GFR is low; diuretics that act by directly inhibiting tubular resorption may also be ineffective in the circumstances. However, the osmotic diuretics retain their effectiveness. Although the GFR is reduced, a substance like mannitol is filtered at the glomerulus and is excreted in the voided urine, dragging water (and sodium) with

it. It is only when the tubules are damaged in addition to reduction in GFR (as happens with nephrotoxic agents or with prolonged, severe, renal ischemia) that the renal tubules become permeable to mannitol, which then loses its capacity to induce diuresis.

MANNITOL: It is a sugar (polyhydroxy aliphatic alcohol) which, when injected intravenously, is not metabolised and is rapidly filtered by the glomeruli. Being nonreabsorbable, it exerts considerable osmotic activity which interferes with the back diffusion of water and reabsorption of sodium in the tubules, causing osmotic diuresis.

To be effective, mannitol has to be administered in sufficiently large doses. Mannitol is not a suitable diuretic in cases of cardiac edema with sodium retention. This is because administration of mannitol increases the ECF volume thus increasing further the load on the already decompensated heart.

It is a useful diuretic in case of barbiturate poisoning to increase the urinary elimination of barbiturate. In such cases, it is infused as a 5-25% solution and the infusion continued as long as the urine output remains good. Water and electrolytes are given concurrently to replace those lost in urine. The infusion is discontinued if no benefit is observed after 200 g of mannitol.

It is also useful in any condition of threatened acute oliguric renal failure from pre-renal causes (e.g. severe gastroenteritis) which result in hypovolemia and hypotension. In such cases, after initial correction of hypovolemia with adequate quantities of fluids, 200 mg. of mannitol per kg. body weight is infused rapidly in 10-15 minutes. If the urine flow rate increases to 100 ml. per hour further mannitol is given to maintain the high urine flow rate. This is believed to prevent the establishment of acute renal failure. If no diuresis occurs after the initial mannitol infusion, established acute renal failure is diagnosed and no more mannitol is given. Mannitol infusion is also started pre-operatively at the time of certain

surgical procedures (aortic surgery, surgery in a deeply jaundiced patient) which are known to increase considerably the risk of acute renal failure. It is also useful in preventing acute oliguric renal failure after severe traumatic injuries and hemolytic transfusion reactions.

Mannitol infusion is also used in the dose of 1.5-2 g/kg (in 30-60 minutes) to reduce raised intracranial tension and to treat cerebral edema.

Although mannitol has been shown to produce certain renal lesions in animals, so far no serious toxicity has been observed in man.

Mannitol is supplied as 25 per cent solution in ampoules of 50 ml. for intravenous use. The details of its administration in acute barbiturate poisoning are discussed in Chapter 6.

ISOSORBIDE : This is a dihydric alcohol formed by removal of two molecules of water from one molecule of sorbitol. It has similar properties as mannitol but is effective orally. However, it is not as efficient as mannitol due to its greater volume of distribution. The drug has been used in the treatment of cirrhotic edema in the dose of 1 to 2 gms per kg. body weight, as 50 per cent solution.

Combination of isosorbide with thiazide diuretics exerts synergistic action.

GLYCEROL : Glycerol is used orally in the dose of 1 to 1.5 g/kg (maximum dose 120 g/day), as a 50 - 75% solution, prior to ophthalmological procedures. Ten percent glycerol in normal saline or in 5% dextrose, given I.V. in the dose of 1.2 gm per kg. body weight, has also been claimed to have certain advantages over mannitol for reducing cerebral edema. It is claimed to avoid the 'rebound edema' said to be common after mannitol. Moreover, it can be used in the presence of dehydration and cardiac failure where mannitol cannot be used. It has been used in the treatment of acute cerebral infarction, given i.v. daily 10% in 500 ml saline for 6 days. Rapid infusion of high concentrations (30%) of glycerol has been reported to cause hemolysis.

SODIUM CHLORIDE: Sodium chloride, given orally or intravenously, can restore urine flow to normal when it is used to treat oliguria caused by salt depletion; intravenous isotonic saline is also valuable to treat oliguria caused by acute hypotension; but then you are using it primarily to restore plasma volume. It is not an important diuretic in any other circumstances.

ACIDIFYING SALTS

AMMONIUM CHLORIDE: It is given orally. After absorption, ammonia is converted by the liver to urea, during which process hydrogen ion is formed.



The hydrogen ion reacts with bicarbonate and other buffers in the ECF. Reduction in bicarbonate changes the $\text{H.HCO}_3/\text{B.HCO}_3$ ratio, thus causing acidosis and a fall in intracellular pH of the tubular cells. This is believed to cause diuresis; the urine becomes acidic. Further, the excess chloride ions from the ECF are filtered by the glomeruli, most of which escape tubular reabsorption, promoting osmotic diuresis.

Diuretic action of ammonium chloride is self-limiting as kidney compensates for the acidosis by producing ammonia and by secreting more hydrogen ions for exchanging with sodium in the tubular fluid. The excess of chloride filtered is excreted in combination with ammonia as ammonium chloride.

Adverse reactions: Ammonium chloride has a nauseating taste. It is a gastric irritant and causes nausea and vomiting. In the presence of renal damage, it can cause severe acidosis, as kidney cannot compensate for it.

Therapeutic uses: The drug is not used as a diuretic. Ammonium chloride is given daily in the dose of 8-12 g., in divided doses, as an urinary acidifying agent. For correcting metabolic alkalosis caused by mercurial diuretics, it can be used in smaller doses (1-2 g. daily).

Other acidifying salts are arginine chloride, ammonium citrate and calcium chloride.

XANTHINES

Pharmacology of xanthines is discussed in Chapter 10. Theophylline is the most effective xanthine diuretic and is generally used as theophylline ethylene diamine (aminophylline). Xanthines probably act by increasing the renal blood flow by both cardiac and vascular actions, as well as by inhibiting tubular reabsorption of sodium. The diuretic action is not much affected by changes in acid base balance. The loss of potassium is usually small.

Aminophylline, however, is a weak diuretic and to be effective, it must be given parenterally. Usually, it is administered intravenously, slowly, in a dose of 0.25-0.50 g., diluted in 10-20 ml. of 5 per cent glucose solution. The drug may cause a striking diuresis when given at the peak of action of a more potent diuretic e.g. 3-4 hours after a thiazide or ½ hour after a member of the very potent group, in a previously refractory patient. The toxicity of aminophylline is discussed elsewhere.

CARBONIC ANHYDRASE INHIBITORS

ACETAZOLAMIDE (Diamox): This drug, a weak diuretic, is unique because of its mechanism of action. It acts by inhibiting the enzyme carbonic anhydrase.

Pharmacological actions:

I. Kidney and electrolytes: The enzyme carbonic anhydrase is present in the renal cortex, gastric mucosa, pancreas, eye, central nervous

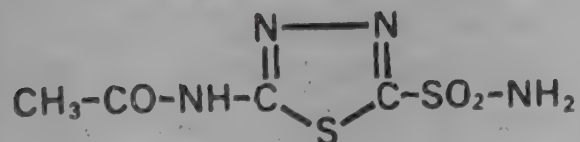


Fig. 35.2 : Acetazolamide

system and red blood cells. It catalyses the reaction:



The enzyme thus plays an important role in the

tubular reabsorption of sodium and bicarbonate by providing carbonic acid which makes available hydrogen ion for exchange with sodium.



Acetazolamide inhibits this enzyme by non-competitive mechanism so that hydrogen ion is not available for sodium exchange, leading to excretion of sodium; along with it water is excreted. It must be noted that major portion of the sodium in the distal tubule is reabsorbed by an active process and $\text{K}^+\text{H}^+/\text{Na}^+$ exchange mechanism controls only a small amount of sodium that accompanies a less diffusible anion, bicarbonate. Normally, the secreted H^+ ion combines with HCO_3^- ion provided by the glomerular filtrate to form H_2CO_3 . This is converted to water and carbon dioxide, the latter being absorbed. Following acetazolamide, due to lack of H^+ ion, bicarbonate will remain in the poorly diffusible form and hence excreted in large amounts. The urine becomes alkaline with a decrease in its titratable acidity. Since exchange of potassium and hydrogen ions with sodium occurs along the same pathway, the decrease in available hydrogen ion may promote more loss of potassium. Acetazolamide, therefore, can cause loss of sodium, bicarbonate and potassium ions. The resulting decrease in the ECF base may cause metabolic acidosis which is accompanied by the loss of diuretic activity. Acetazolamide is thus a self-limiting diuretic. Its action is markedly decreased by acidifying salts while it is enhanced in the presence of metabolic alkalosis.

II. Eye : Carbonic anhydrase present in various intraocular structures is believed to be important in the production of aqueous humor, which has a high bicarbonate content. Acetazolamide reduces the intraocular tension, probably by inhibiting this enzyme.

III. C.N.S. action : Acetazolamide decreases the C.S.F. formation. For its antiepileptic action, see Chapter 7.

IV. Other actions : The drug depresses the thyroidal uptake of iodine and is also claimed

to benefit patients with pulmonary emphysema by acting on carbon dioxide transport system.

Absorption, fate and excretion : Acetazolamide is given orally and is well absorbed. It is not metabolised but is excreted almost completely by the kidney within 24 hours.

Adverse reactions : As discussed above, it can cause metabolic acidosis and hypokalemia. In fact, sometimes it produces excessive potassium loss without causing significant sodium loss. The metabolic acidosis is dangerous in the presence of kidney damage. Occasionally, it can cause drowsiness and paraesthesiae. Being structurally related to sulfonamides, rarely, it can cause other adverse effects like skin rashes, blood dyscrasias, crystalluria and kidney damage. Salicylates enhance the toxicity of acetazolamide by inhibiting its plasma protein binding and by interfering with its renal tubular secretion.

Preparation and dosage : Acetazolamide 0.25 g. tablet; dose : 1-2 tablets as a single dose. Sodium acetazolamide can be given parenterally.

Therapeutic uses: The use of acetazolamide is now restricted to the treatment of glaucoma, resistant epilepsy and the syndrome of periodic paralysis.

It has also been used successfully in the prophylaxis of acute mountain sickness. In mild cases of mountain sickness, a regimen of rest, frequent small meals is all that is necessary. Sedatives should be avoided. The drugs which have been found to be useful in the management of mountain sickness are acetazolamide and dexamethasone.

Acetazolamide causes hyperchloremic metabolic acidosis. Respiration stimulated by acidosis leads to a compensatory respiratory alkalosis. Pre-treatment with this drug, thus, mimics the acclimated state of acid-base balance and causes higher oxygen tension in subjects. It is used prophylactically in the dose of 250 mg every eight hours begun the day before the ascent and continued for at least 5 days at the high altitude. Adverse effects are mild. Paresthesia, G. I. disturbances and somnolence are frequent. Subject

may experience flat taste of carbonated beverages.

Dexamethasone, in the dose of 2 to 4 mg. every six hours begun the day of the ascent, and continued for 3 days at high altitude and then tapered off is also useful and may be used prophylactically as an alternative to acetazolamide. It is, however, highly effective in the treatment of brain edema. Depending upon the severity of this condition, it is used in the dose of 4 mg every 6 hours orally for one to three days and then tapered over 5 days. Doses of acetazolamide up to 1.5 g. may be required for effective treatment. Hence, descent remains the most unequivocally successful treatment for acute mountain sickness and is mandatory in severe cases. Oxygen therapy, if available, would help.

Aspirin, amphetamines, codeine and phenytoin have not proved to be beneficial in the prevention or treatment of acute mountain sickness.

DICHLORPHENAMIDE: This drug has a greater duration of action than acetazolamide and in addition, also causes chloride depletion. It is used in the daily dose of 50 to 200 mg. in the treatment of chronic respiratory insufficiency associated with chronic bronchitis and emphysema, and in the treatment of glaucoma.

ETHOZOLAMIDE : This compound is twice as potent as acetazolamide and has similar uses.

METHAZOLAMIDE: This drug, about 30-60 per cent more potent than acetazolamide, is mainly used in the long-term treatment of glaucoma. Dose, 50 to 100 mg., twice or thrice daily.

BENZOTHIADIAZINES

Introduction of thiazide diuretics revolutionized the oral diuretic therapy, since before chlorothiazide, no effective and reliable oral diuretic was available. Synthesis of various thiazide

compounds stems from the original observation by Southworth (1937) that sulfanilamide, an antibacterial drug, possesses a mild diuretic activity. This was later shown to be related to its carbonic anhydrase inhibiting action. Interestingly, chlorothiazide, synthesized as one of the carbonic anhydrase inhibitor drugs, revealed marked diuretic activity in doses that did not significantly inhibit the enzyme carbonic anhydrase. Since then, various thiazide diuretics with a similar mechanism of action have been introduced. They differ from each other only in their minimal effective doses and the duration of their activity (Fig. 35.3); their maximum diuretic effects are equivalent.

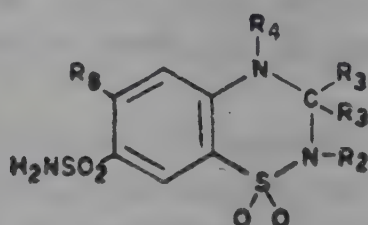


Fig. 35.3 : Benzothiadiazine nucleus.

Pharmacological actions:

(a) **Kidney and electrolytes:** These drugs probably act at a number of sites along the nephron. They prevent the reabsorption of sodium and chloride. They are believed to act mainly on the site proximal to the sodium and potassium exchange region in the distal tubule (site III, Fig. 35.1). The glomerular filtration rate is not affected. Chlorothiazide has a weak carbonic anhydrase activity and hence, in therapeutic doses it can cause some loss of bicarbonate. The newer thiazide diuretics, however, have a negligible carbonic anhydrase inhibitory action and they do not significantly increase the bicarbonate loss in therapeutic doses.

Initially, the drug causes a diminution in sodium reabsorption in the distal tubule and a gradual reduction in the ECF volume. When the ECF volume falls to slightly below normal the reabsorption of sodium from the proximal tubule is stimulated, resulting in diminished amount of sodium delivered into the distal tubule. This

causes a decrease in diuretic activity and resistance.

Because of the marked inhibitory action on sodium reabsorption, a large amount of sodium is made available to the distal segment where exchange of potassium with sodium takes place. This probably causes increased potassium loss, particularly in the presence of excessive aldosterone which is known to stimulate this exchange mechanism.

Excessive renal loss of sodium and chloride may cause hyponatremia and hypochloremia; excessive potassium loss can cause hypokalemia, thus leading to hypokalemic hypochloremic alkalosis.

(b) **Hypotensive action :** Thiazides produce a mild hypotensive effect partly due to their action on sodium metabolism and partly due to their direct action on blood vessels. Their use in the treatment of hypertension is discussed in Chapter 26.

(c) **Metabolic actions:** Prolonged therapy with thiazide diuretics may cause hyperglycemia and glycosuria. Fortunately, withdrawal of the drug is followed by prompt recovery. These drugs can unmask or aggravate the pre-existing diabetes mellitus. Diazoxide, a thiazide derivative which has potent hyperglycemic action, has been used in the treatment of hypoglycemia.

The mechanism by which benzothiadiazines cause hyperglycemia is not known. Catecholamine release, secondary to volume depletion, a direct inhibition of insulin release and hypokalemia are the possible mechanisms. Polyuria and weight loss during diuretic therapy can be due to either diuretic effect alone or to the diabetogenic effect as well; the latter may be easily overlooked. Rarely, the hyperglycemia may be severe enough to lead to hyperglycemic, hyperosmolar, non-ketotic coma in diabetics, especially those in the older age groups.

Thiazides also decrease the excretion of uric acid, thus raising uric acid concentration of plasma. Usually, this is asymptomatic but, occasionally, it can precipitate attacks of gouty arthritis.

tis. They also decrease urinary excretion of calcium. Serum cholesterol and triglycerides may increase slightly; however, this has hardly any significance as the elevation is not persistent beyond 6-12 months of treatment.

In patients with diabetes insipidus, especially the nephrogenic type, thiazides decrease urinary volume. This aspect is discussed later.

Absorption, fate and excretion: Benzothiadiazine diuretics are well absorbed from the intestines and the effect starts within one hour after oral administration. They are distributed throughout the extracellular space and are relatively concentrated in the kidney. These drugs can cross the placental barrier. Like other organic acids, thiazides are secreted by the tubules and excreted in urine. The excretion rate varies with the drug and certain slowly excreted derivatives like polythiazide, bendroflumethiazide and trichlormethiazide have prolonged action. The long acting benzothiadiazines are long acting because of their (a) greater plasma protein binding and (b) greater lipid solubility. The latter property results in their initial larger volume of distribution in the body with subsequent back diffusion.

Adverse reactions : Apart from electrolyte disturbances such as hypokalemic and hypochloremic alkalosis, these drugs have remarkably few serious toxic effects. Occasionally, they can cause allergic reactions like thrombocytopenic purpura, dermatitis and blood dyscrasias.

In the presence of renal and hepatic insufficiency, these drugs may precipitate renal failure or hepatic coma. This is usually attributed to the development of hypokalemia and alkalosis.

Preparations and dosage : Various preparations available are listed in Table 35.1.

Therapeutic uses : Thiazides produce effective diuresis in most of the patients with sodium retention and edema. Since there is no special advantage in using any particular preparation, the cheapest of these should be the drug of first

choice. Dosage has to be adjusted in individual cases depending upon the response. Occasionally, patients may develop resistance to these drugs. In majority of such cases, hypokalemia may be present which needs correction; for this purpose, potassium chloride is commonly used. However, enteric coated tablets of thiazides containing potassium chloride should not be used as these have been implicated in the causation of intestinal ulcerations. Excessive potassium loss can be prevented by combining thiazide drugs with spironolactone or triameterene. As the maximum diuretic effect of all benzothiadiazines is similar, a patient resistant to the maximum dose of one drug from this group is unlikely to respond to another from the same group. He is, however, likely to respond to a drug from the very potent group.

Hydrochlorothiazide, in the dose of 50 mg twice a day, has been used to reduce the frequency of renal calculi formation in patients with essential hypercalciuria.

CHLORTHALIDONE (Hythalon): This is a phthalimidine derivative with some similarity in structure to the thiazide group and has similar pharmacological actions. The drug is absorbed slowly, and is not significantly metabolized in the body. Further, it remains preferentially bound to renal tissue for prolonged periods. Its duration of action, therefore, is longer, upto 48 hours or more. As a diuretic, it offers no significant advantage over the thiazides, but may be preferred in the treatment of hypertension. It is more liable to cause hypokalemia than the thiazides. It has recently been reported to be useful in the treatment of hypoparathyroidism where it corrects hypocalcemia without the danger of causing hypercalcemia which is inherent in vitamin D therapy of this condition.

Indapamide and xipamid, drugs related chemically to chlorthalidone, are diuretics which are used in the treatment of hypertension (see Chapter 26).

Table 35.1 : Commonly used Benzothiadiazine and other diuretics

Name	Tablet mg.	Daily dose mg.	Duration of action hours
Chlorothiazide (Chlorotride)	250, 500	500 to 1000 Children : 20 mg./kg.	6 to 12
Hydrochlorothiazide (Esidrex)	25, 50	25 to 200 Children: 2 mg./kg.	12 or more
Hydroflumethiazide (Naclex)	50	25 to 200	18 to 24
Benzthiazide (Fovane)	25	50 to 200	12 to 18
Cyclopenthiazide (Navidrex)	0.5	0.5-1	18 to 24
Bendroflumethiazide (Neo-NaClex)	2.5, 5	2.5 to 5	18 to 24
Polythiazide (Nephрил)	1, 2, 4	2 to 4	24 to 48
Chlorthalidone (Hygroton, Hythaltan)	100	50 to 200	48 to 72
Quinethazone	50	50 to 200	18 to 24
Metolazone (Zaroxilin)	5	5 to 10	18 to 24

CHLOREXOLONE (Nefrolan) : This is another phthalimidine derivative claimed to be more effective than chlorothiazide on weight basis. Given orally, the maximum diuresis is seen at 2-4 hours and it lasts for 12-24 hours. The electrolyte excretion pattern and other actions are similar to thiazides. The drug has no distinct advantages over the established thiazide compounds. Dose : Oral 25-100 mg.

CLOPAMIDE : This diuretic, with a duration of action similar to bendroflumethiazide, is administered in a single daily dose of 20 to 60 mg. in the morning, on alternate days. It appears to be well tolerated and blood urea levels are not affected during treatment. Apart from its longer duration of action (18-24 hr.) it appears to have no advantage over the thiazides.

QUINAZOLINONES : Quinethazone and Metolazone belong to this group. These compounds have diuretic characteristics similar to those of benzothiadiazines, and offer no special advantages.

ORGANIC MERCURIAL DIURETICS

Introduction of organic mercurial compounds as diuretics came from the clinical observation of an unexpected adverse reaction. A medical student from Vienna, who could not obtain the prescribed mercurial preparation ordered by his superior for a nonedematous girl suffering from congenital syphilis, injected an organic mercurial compound, Merbaphen, which produced a conspicuous rise in the urine volume after each injection. Subsequently, several organic mercurials were synthesized and the structure activity relationship was studied.

Organic mercurial compounds, given parenterally, are reasonably safe and effective diuretics. However they are ineffective orally and sometimes cause renal impairment during parenteral therapy. For details, see the earlier editions of the book.

LOOP DIURETICS

FRUSEMIDE (Furosemide, Lasix, Kinex) :

It is a potent, oral, non-mercurial diuretic, possessing a halogenated sulfamoyl benzene ring common to thiazide diuretics (Fig. 35.4).

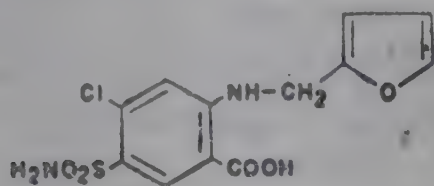


Fig. 35.4 : Frusemide. Note the sulfamoyl benzene ring.

Pharmacological actions:

I. Kidney and electrolytes: On oral administration, the intense diuretic action starts within an hour and is complete by 4-6 hours. It produces more chloride loss than sodium loss and it depresses both urinary dilution and concentration mechanisms. Frusemide produces further increase in diuresis in patients given maximum therapeutic doses of thiazides but thiazides do not enhance the frusemide activity. Available evidence suggests that frusemide acts along the entire nephron (sites II and III in Fig. 35.1) including the loop of Henle with the exception only of the distal site where Na^+ is exchanged for K^+ and H^+ . Hence unlike thiazides, urinary excretion of Na^+ may continue uninterrupted even when the patient's ECF volume has been severely depleted. In therapeutic doses, the drug has little effect on carbonic anhydrase and bicarbonate loss is not marked. It, however causes increased phosphate excretion.

Frusemide enhances potassium excretion. The absolute loss of urinary potassium is as great as that following thiazides and higher than that with mercurials.

Frusemide causes little change in the urinary pH and its diuretic response does not appear to be particularly limited by the existing state of electrolyte or acid-base balance.

Excessive loss of chloride may lead to hypochloremic alkalosis as with mercurials. Associated potassium loss may cause hypokalemia.

After intravenous administration, furosemide

produces an increase in renal blood flow. It also produces a redistribution of blood away from the lungs into the capacitance, peripheral venous vessels; it fails to produce this action in anephric subjects and in patients on NSAID. Furosemide increases the P.G. synthesis in the kidneys; the PGE_2 has a local, protective vasodilator effect. Under normal circumstances, this PG system is dormant but becomes operative in times of physiological or pharmacological stress and counter the intra-renal vasoconstriction which would otherwise occur.

II. Other actions : Like thiazides, frusemide can cause an increase in blood uric acid level and disturbances of glucose tolerance; rise in blood urea has also been reported. Calcium and magnesium excretion is increased significantly. Its effects on the blood pressure are probably comparable to those of thiazide diuretics. Intravenous frusemide has been shown to have important peripheral vascular effects leading to pooling of blood in the peripheral deep veins. This effect is more rapid than the diuretic effect and may be more important than the latter in the treatment of acute left ventricular failure with pulmonary edema.

Absorption, fate and excretion : The drug is rapidly absorbed from the gastrointestinal tract and is excreted within 4 hours, largely unchanged, regardless of the route of administration, both by glomerular filtration and tubular secretion. The onset of action is quick and the duration short. On its intravenous administration, the diuresis begins within 2 minutes and lasts for 2-3 hours. Given orally, the effect is complete within 6 hours. It is best given in a single dose.

Adverse reactions : As it is a powerful diuretic, its unintelligent use can precipitate serious electrolyte and water disturbances due to excessive loss of sodium, potassium, chloride and water. A patient may complain of weakness, fatigue, dizziness, and cramps; orthostatic hypotension can occur. Excessively rapid diuresis in elderly patients may precipitate acute urinary

retention. Cardiac arrest following intravenous frusemide and sudden death following its intramuscular administration have been reported. The drug can precipitate hepatic coma in the presence of liver disease. Other adverse reactions include skin rashes, nausea, diarrhoea and rarely acute pancreatitis, thrombocytopenia and neutropenia. Serious liver or bone marrow damage is rare. The drug can produce hyperuricemia and unmask latent diabetes mellitus.

Hearing loss, usually transient, but sometimes permanent with or without tinnitus have been reported following very large doses of frusemide in patients with severe renal failure.

Preparations and dosage: Frusemide tablet 40 mg., Frusemide injection, 20 mg. in 2 ml. Dose: 40-100 mg. daily depending upon the severity of the edema.

Therapeutic uses: Given orally frusemide is a very effective and usually a safe diuretic. However, it has no distinct advantage over thiazide diuretics in the treatment of moderate edema. It is more useful in cases with severe edema and those resistant to other established diuretics. Not all resistant cases, however, respond to frusemide.

Given intravenously, it is very useful in patients with pulmonary edema. It is also used to induce forced diuresis in the treatment of barbiturate poisoning. It is sometime effective in the presence of marked decrease in GFR (as low as 2 ml/minute) and in mannitol resistant acute oliguria; in such cases, larger doses are generally necessary.

The dose response curve with frusemide shows a steep rise and very large doses (2000 mg. daily) have been used in patients with advanced renal failure. Since the drug continues to act even in the presence of electrolyte and acid-base disturbances, close monitoring of the therapeutic response and blood chemistry is very essential. The drug can be combined with triamterene or spironolactone to prevent excessive potassium loss.

Intravenous furosemide, together with normal saline infusion, is valuable in the emergency

management of hypercalcemia.

Frusemide cannot be recommended for antihypertensive therapy because of high dose requirements, short duration of action and its high diuretic potential. In this respect, well established thiazides are to be preferred.

MEFRUSIDE: This congener of frusemide has been claimed to be more potent than frusemide in equal doses. The pharmacological actions, however, resemble more to that of benzothiadiazines than frusemide. It is given orally in the dose of 12.5-50 mg. The diuretic action lasts for 20-24 hours.

BUMETANIDE (Burinex): This diuretic is chemically 3-n-butylamino-4-phenoxy-sulphamoyl benzoic acid. Its onset and duration of action and its effects on electrolyte excretion are similar to those of frusemide. It is effective orally. It has no special advantages except that 1 mg. of bumetanide equals 40 mg. of frusemide in its diuretic potency; this of course is hardly an advantage. Interestingly the drug is virtually ineffective in the rat where it is extensively metabolized.

ETHACRYNIC ACID (Edecrin) : Since mercurials were thought to produce the diuretic action by combining with sulfhydryl groups of the tubular enzymes, newer compounds with a similar biochemical action were synthesized. Of these, ethacrynic acid, an unsaturated ketone derivative of phenoxyacetic acid, is a very potent oral diuretic like frusemide. Chemically, it is unrelated to other diuretic drugs. The acid is sparingly soluble in water but its sodium salt is water soluble.

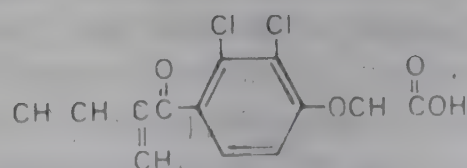


Fig. 35.5 : Ethacrynic acid

Pharmacological actions : Although ethacrynic acid differs chemically from frusemide, the two compounds appear to be remarkably similar in their diuretic effects. The renal actions of ethacrynic acid are similar to those produced by frusemide (site II and III in Fig. 35.1). When given orally, the maximum diuresis occurs within 2-3 hours while on intravenous administration the effect starts within a few minutes and is complete within 1-2 hours. Like frusemide, it can cause hypochloremic alkalosis, potassium depletion, hyperuricemia and even hyperglycemia. It also increases the excretion of calcium and magnesium.

Like frusemide, the drug is believed to act at various sites in the nephron, including the ascending limb of the loop of Henle.

Absorption, fate and excretion : It is given in a single dose, after meals. Administered orally, it is rapidly absorbed and rapidly excreted by the kidney largely unchanged and as cysteine complex. Some amount is also found in bile.

Adverse reactions: Ethacrynic acid besides causing various electrolyte and metabolic disturbances like frusemide, produces other toxic effects. It sometimes causes anorexia, nausea, vomiting and diarrhoea. Rarely, skin rashes, thrombocytopenia, agranulocytosis and gastrointestinal bleeding especially on intravenous use have been reported. Acute vertigo, deafness and tinnitus may also occur following large doses.

Preparations and dosage: (1) Ethacrynic acid tablets 50 mg. The optimum dose varies from 50 to 200 mg. In children, an initial dose of 25 mg. is recommended. (2) Sodium ethacrynate injection, dose 0.5 and 1 mg. per kg. in adults. The drug is administered, diluted with 50 ml of normal saline or 5 per cent dextrose.

Therapeutic uses: Although it can be given in various types of edematous states because of high potency and rapidity of action, it is most useful in severe or resistant cases and in patients with pulmonary edema.

POTASSIUM SPARING DIURETICS

SPIRONOLACTONE (Aldactone): This is a commonly employed aldosterone antagonist. Spironolactone is a steroid with structural similarity to aldosterone. It acts by competitive antagonism of aldosterone, in the distal part of the nephron, thereby preventing the potassium secretion and decreasing the sodium reabsorption. Obviously, the drug does not produce significant action in normal individuals or in those cases of edema which are not associated with rise in aldosterone concentration. Even in edematous states associated with an excess of circulatory aldosterone, its diuretic action is weak.

Spironolactone is given orally in a total daily dose of 100 mg. It has a cumulative effect and full response is observed only after a few days of therapy. Given alone, it may cause a weak diuretic response but along with other diuretic agents such as thiazides, it causes diuresis without producing significant loss of potassium.

Adverse reactions: No serious toxic effects have been reported even after long term use of this drug. Occasionally, it may cause drowsiness, decreased libido, gynecomastia and menstrual irregularity. The drug has antiandrogenic activity at the receptor level and has been shown to affect both gonadal and adrenal steroidogenesis. In the presence of renal insufficiency, it will cause retention of potassium and hyperkalemia. Spironolactone may increase blood urea nitrogen and serum uric acid levels.

Aspirin has been reported to interact with spironolactone and to interfere with its action. Aspirin containing preparations, therefore, are better avoided during spironolactone therapy.

Preparation and dosage: Spironolactone is supplied as a microcrystalline preparation, 25 mg. tablet. Dose: 25 mg. two or four times a day.

Therapeutic uses : Its important use is in the treatment of primary aldosteronism (Conn's Syndrome) where it has been used as an alterna-

tive to bilateral adrenalectomy. Given orally, the drug corrects the electrolyte abnormalities and reduces blood pressure. It is useful in cases of refractory edema, where it is used in combination with other potent diuretics. Its use in various types of edema is discussed later in this chapter. It is also useful in some cases of resistant hypertension. Its use in hirsutism is discussed in Chapter 64.

POTASSIUM CANREONATE: This aldosterone antagonist has similar uses as spironolactone but can be given parenterally. Its metabolite canrenone is also a metabolite of spironolactone. It is available as injections containing 10 mg./ml. in 20 ml. ampoules and is given intravenously, slowly, upto 500 mg. per day, in divided doses.

TRIAMTERENE (Dytac) : This drug, when given orally, increases the excretion of water, sodium, chloride and bicarbonate but unlike other diuretics, it depresses the excretion of potassium. In this respect, it resembles the aldosterone antagonist spironolactone. After oral administration in man, the peak effect is reached in about 2 hours and the action is over in about 10 hours.

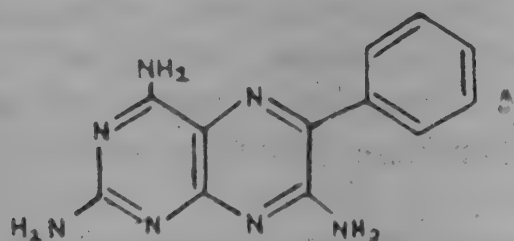


Fig. 35.6 : Triamterene

The mechanism of action of triamterene on potassium transport is not clear but it has probably a direct action on the distal tubule of the nephron, as the drug produces this effect even in adrenalectomised animals. Unlike spironolactone, triamterene does not influence the sodium potassium ratio of the saliva. Further, combination of triamterene and spironolactone produces more marked natriuretic effect than the maximally effective dose of triamterene given alone.

It is not, therefore, an aldosterone antagonist. The drug also increases the excretion of bicarbonate and has been shown to be effective in the presence of experimental acidosis as well as alkalosis. The drug increases the excretion of uric acid and does not produce hyperglycemia.

Adverse reactions : So far, no serious toxic effects have been noted. Besides causing hyperkalemia, the drug may cause troublesome diarrhoea. Occasionally, skin rash and dryness of mouth have been noted. It may cause a rise in blood urea level during therapy.

Preparation and dosage: It is administered orally in the dose of 100-200 mg.

Therapeutic uses : Triamterene is a weak diuretic and is not recommended as an oral diuretic of choice. However, it can enhance the actions of other diuretics and hence, can be combined to increase the natriuretic effect while decreasing the potassium loss due to other diuretics, particularly in the long term management of persistent edema due to nephrotic syndrome and hepatic cirrhosis.

The drug has also been used in a condition called 'pseudoaldosteronism', a familial renal disorder characterised by hypertension, and hypokalemia but not associated with increased aldosterone secretion. In such patients, spironolactone is not of much use as the aldosterone secretion is subnormal.

AMILORIDE HYDROCHLORIDE: This compound, a guanidine derivative with a weak diuretic activity, is given orally in the dose of 10 mg. It has pharmacological actions similar to triamterene. It produces a much weaker diuretic effect than 50 mg. of hydrochlorothiazide. However, like triamterene it prevents potassium loss. It probably acts at the same site of the kidney as triamterene. The plasma half life is about 6 hours. It is excreted unchanged in the urine. On weight basis it is more potent than triamterene. It is given in the dose of 10-20 mg. daily, usually in combination with other diuretics acting more proximally in the nephron.

Diuretic therapy: The important indications for diuretic therapy are:

- I. Edema associated with sodium retention such as cardiac, hepatic or renal edema.
- II. Pulmonary edema.
- III. Drug poisoning such as due to barbiturates and salicylates (See Chapter 6).
- IV. Acute renal failure.

MANAGEMENT OF EDEMA

Increase in extracellular sodium and fluid volume leads to the development of edema. This could occur due to either an excessive intake or decreased excretion of sodium and water. Experimentally, it is very difficult to produce edema in the presence of normal renal function and the edematous states observed in practice are mostly due to decreased rate of renal excretion of sodium and water.

Various factors are involved in promoting excessive sodium retention by the kidneys. In a given case more than one factor may be involved. The important ones are:

- (1) decreased cardiac output and G.F.R.
- (2) increased levels of aldosterone as in edema due to hepatic cirrhosis.
- (3) intrinsic renal disease such as acute nephritis.
- (4) reduction in plasma colloids as in hypoproteinemic states (nutritional edema and nephrotic syndrome).

Although the treatment of underlying pathology is important in all such cases, great relief can be obtained by using proper diuretics. Edema can be treated by:

- (a) ensuring adequate renal perfusion, by improving cardiac efficiency, as in cardiac edema,
- (b) restricting sodium intake or preventing its absorption from gastrointestinal tract by using ion exchange resins, and
- (c) by promoting sodium and water excretion by using diuretics.

Usually, these approaches are combined.

CATION EXCHANGE RESINS: Ion exchange resins are synthetic, macro-molecular compounds. Two types of resins are available, the anion exchange resins and the cation exchange resins. The anion exchange resins contain a basic group and were formerly used as gastric antacids. The cation exchange resins contain an acidic group and their cations can be exchanged for ions with a positive charge.

The cation exchange resins, when administered by mouth, exchange their H^+ ions for Na^+ ions. The resultant compound is not absorbed, thereby preventing the absorption of sodium from the small intestine. Potassium is also exchanged along with sodium, resulting in a significant loss of potassium in feces along with sodium.

Prolonged therapy with cation exchange resins results in a significant absorption of H^+ ions from the gastrointestinal tract leading to metabolic acidosis.

Besides hypokalemia and metabolic acidosis, the resins often produce nausea, vomiting and diarrhoea and may cause fecal impaction. The dose needed is very bulky. Hence, they are rarely used in therapy.

The cation exchange resins available for therapy are:

- (i) Sodium polystyrene sulfonate, used for removal of potassium, dose 15 to 60 g. daily.
- (ii) Carbacrylamine resins, used for removal of sodium, dose 40 to 65 g. daily.

Cardiac edema: This is due to the failure of the heart as a pump, leading to a fall in the cardiac output and an inadequate renal perfusion. Hence, unless the cardiac function is improved and adequate renal perfusion is restored, no diuretic acting on the renal tubules can cause worthwhile diuresis. Adequate GFR is ensured by:

- (i) increasing the cardiac output by using digitalis and by
- (ii) decreasing the tissue demand for blood by such measures as rest and other appropriate treatment of the underlying disease such as hyperthyroidism, anemia, beriberi or hypertension. Re-

striction of sodium intake and diuresis are usually combined with the primary therapy of the cause.

In mild and early congestive cardiac failure, a moderately potent drug such as a thiazide is preferred to frusemide or ethacrynic acid. The latter cause abrupt diuresis with contraction of plasma volume because the rate of transfer of fluid from the E.C.F. into the plasma lags behind the urinary loss of fluid. This results in secondary hyperaldosteronism. For the same reason, intermittent use of a diuretic (say 2-3 times a week) is to be preferred to its daily administration. When planning continuous diuretic therapy, spironolactone may be combined with the primary diuretic right from the beginning of therapy with advantage, instead of waiting for resistance due to hyperaldosteronism. As the disease progresses, increasing doses of thiazides and their more frequent administration inevitably culminate in the use of frusemide; this, in turn, has to be used in progressively larger doses. However, the routine use of the very potent diuretics in all cases of cardiac failure from the beginning is to be strongly deprecated. Patients who are resistant to diuretics are likely to benefit from administration of captopril (see Chapter 26).

Cirrhotic edema and ascites: This is believed to be due to increased portal venous pressure, decreased plasma colloid osmotic pressure following hypoalbuminemia and secondary rise in aldosterone secretion. The treatment, therefore, would be bed rest to restrict sodium intake and in severe cases to use diuretics acting on renal tubules along with aldosterone antagonist. As compared with cardiac edema, the danger of precipitating hypokalemia and azotemia with diuretic therapy is higher in cirrhotic edema; the chances of precipitating hepatic encephalopathy are also high. Hence, the diuretic therapy in a cirrhotic patient with ascites should be undertaken under supervision in a hospital with repeated checks on serum electrolytes. The dose used should be the smallest possible one and oral potassium supplements should be given. The currently recommended regime is as follows:

begin with bed rest, restriction of sodium intake (to 20 mEq/day) and provided the blood urea is normal, oral potassium supplements in large doses (100 mEq/day). After 4-5 days, spironolactone is added; potassium supplement is continued in cirrhotic patients unlike in patients with edema due to other causes. If adequate diuresis does not occur in 5 days, a potent diuretic is added e.g. frusemide in doses up to 120 mg/day. This regime is preferable to one using spironolactone after the patient has become resistant to frusemide.

Seriously ill cirrhotic patients with ascites should not be treated too vigorously, as this may precipitate hepatic coma, azotemia and death.

Renal edema: Diuretics are ineffective in treating edema of acute nephritis. In patients with nephrotic syndrome, benzothiadiazine drugs, chlorthalidone, frusemide and ethacrynic acid have all been shown to be effective, though the response varies. These drugs should be combined with bed rest and aminophylline. Although the nephrotic syndrome is often associated with secondary aldosteronism, addition of spironolactone is not always rewarding. Corticosteroids such as hydrocortisone or their synthetic analogues, given as short courses over a few days, have been shown to benefit many cases; but relapses are common, and the effect on proteinuria is variable. Their mechanism of action is unknown. Glucocorticoids are more effective in children than in adults. In severe cases of nephrotic edema, infusion of salt poor albumin (20 to 40 g.) is sometimes successful.

Renal edema in patients with chronic renal failure is usually refractory to thiazide diuretics but frusemide or ethacrynic acid are often effective. If they fail, the addition of triamterene or spironolactone may prove useful; this, however, should be done cautiously. Where oral therapy has failed, large doses of intravenous frusemide may be helpful in some patients. Diuretic therapy is combined with the restriction of sodium intake.

Nutritional edema: This is mainly due to

lack of serum proteins and it responds to increased protein intake. Diuretics are usually not necessary. In severe cases, diuretics may be used to obtain temporary relief from the edema; vigorous diuretic therapy, however, is dangerous and should be avoided.

Acute renal failure: The use of mannitol in the prophylaxis and evaluation of acute oliguria has already been discussed. The mechanism by which mannitol prevents the establishment of acute renal failure is not clear but the maintenance of an adequate flow of relatively dilute urine appears to be the most important single factor. This may act by reducing the concentration of the noxious agent in the renal tubules. Additional factors may be (a) improvement of the G.F.R. by mannitol acting as a temporary plasma expander and (b) reduction of cellular swelling and improvement of renal blood flow because of the increased plasma osmolality.

The use of the very potent diuretics (frusemide, ethacrynic acid) for the same purpose is more controversial. They are effective in some patients when used in very large doses. Some workers, however, recommend that they are better avoided in these circumstances as there is some experimental evidence that they may actually aggravate the renal damage.

Choice of a diuretic: The choice of a diuretic in the treatment of edema would depend on:

- (1) nature of the disease,
- (2) potency of the drug,
- (3) biochemical changes associated with its use,
- (4) possibility of development of tolerance,
- (5) convenience of administration, and
- (6) cost of therapy.

Majority of the patients with edema respond dramatically to relatively small doses of any moderately effective diuretic agent, and thiazides, being orally effective, reasonably safe and cheap drugs, are to be preferred for routine use in hospital as well as in domiciliary practice. Only in severe cases where quick and vigorous re-

sponse is needed, and this is so only in a few cases, potent diuretics like frusemide or ethacrynic acid may be employed. The thiazide diuretics are usually ineffective once the GFR has fallen below 20 ml/min. Frusemide and similar potent diuretics remain effective until the GFR has fallen below 3 ml/min, but they often have to be used in very large doses that could be toxic. With such potent diuretics, the likelihood of serious electrolyte disturbances is greater. Vigorous treatment with potent diuretics, coupled with strict restriction of sodium intake to clear the edema may lead to rapid development of body electrolyte disturbances. Hence, potent diuretics should be reserved for refractory or severe cases.

Combination of diuretics: There is no advantage in routinely combining diuretics, particularly drugs from the same group. The diuretic response to frusemide or ethacrynic acid may not increase by adding a second drug. Routinely, in a majority of the cases, a single diuretic agent given in adequate doses is all that is necessary. Only in some cases, where a single drug is ineffective, another diuretic may be added or substituted. Usually, a potent drug like frusemide and ethacrynic acid, given alone will produce adequate diuresis when other drugs have failed. Diuretic combinations are, however, recommended to prevent or counter certain body electrolyte disturbances. Thus,

(1) mercurials are combined with ammonium chloride or acetazolamide to correct the chloride loss and alkalosis,

(2) thiazides are given with triamterene to decrease potassium loss or with spironolactone to counteract excessive aldosterone action. Triamterene and spironolactone should not be combined, as both these drugs promote potassium retention and may thus cause serious hyperkalemia.

(3) Concurrent use of a thiazide and a loop diuretic has been reported to control refractory edema in azotemic hypertensive patients.

Glucocorticoids are combined with diuretics

in patients with nephrotic edema and in edematous cases that are refractory to conventional diuretics. *It is important to remember that the combination of steroid, a diuretic and existing secondary aldosteronism may lead to severe potassium loss and hypokalemia.*

If a combination is to be used, each agent should be given in an optimally effective dose adjusted according to the patient's response; ready-made combinations with fixed dose ratios of different drugs should be avoided.

COMPLICATIONS OF DIURETIC THERAPY

Diuretic therapy, no doubt, is very effective and many times life saving. However, if carried out vigorously and under certain circumstances, it can produce various complications. These are:

(a) **Allergic reactions:** These include various types of skin eruptions, urticaria, occasional blood dyscrasias and rarely interstitial nephritis. Such reactions are usually confined to a single drug or class of drugs. In such circumstances, a drug from another group may be substituted.

(b) **Disturbances of electrolyte balance** (see Table 35.2): These occur more commonly and are usually predictable. These include:

(i) **Acute sodium depletion and hypovolemia:** This is a relatively common complication especially following the powerful loop diuretics and may be pronounced in hot weather, in patients on

sodium restriction and in patients with undetected renal disease. The patient who improves dramatically initially with a diuretic suddenly becomes lethargic and sleepy. Signs of dehydration are present. Increasing the sodium intake reverses this condition. In severe cases, parenteral administration of sodium chloride may be necessary. The treatment of sodium depletion is discussed in Chapter 33.

(ii) **Chronic sodium depletion:** This is less common and is characterised by lethargy, weakness and disorientation. Absence of demonstrable edema along with a low serum sodium level is the cardinal requirement for the diagnosis of chronic sodium depletion. This condition should be distinguished from the much more severe condition of dilution hyponatremia discussed below.

(iii) **Potassium depletion and hypokalemia:** This occurs during long term use of benzothiadiazines, frusemide and ethacrynic acid. It is especially liable to occur (a) when these drugs are used in large doses continuously rather than in small doses, intermittently; (b) when the diuresis is very brisk rather than gentle and the resultant contraction of plasma volume causes secondary hyperaldosteronism; (c) when the patient receives glucocorticoids, carbenoxone or powerful purgatives at the same time; (d) in diabetics; (e) in elderly patients and the chronically sick who may have anorexia and may not eat properly;

Table 35.2 : Electrolyte excretion pattern following diuretics

Drug	Urinary electrolytes				Effect of	
	Na	K	Cl	HCO ₃	Acidosis	Alkalosis
Organic Mercurials	+	+	+	+	--	Decreased
Acetazolamide	+	+	+	+	Decreased	--
Thiazides	+	+	+	+	Decreased	--
Frusemide	+	+	+	+	--	--
Ethacrynic acid	+	+	+	+	--	--
Spirolactone	+	*	+	+	--	--
Triamterene	+	*	+	+	--	--
Aminophylline	+	--	+	--	Decreased	--
Mannitol	+	+	+	+	--	--

*denotes potassium retention.

-- denotes no change.

and (f) in states (such as cirrhosis of liver) with high circulating levels of aldosterone to begin with.

By itself it can impair renal function and is dangerous to patients receiving digitalis. Diuretic induced hypokalemia can cause life threatening arrhythmias in patients taking drugs which prolong QT interval (quinidine, procainamide, prenylamine and amiodarone). The risk appears to be prohibitively high with prenylamine. It can be prevented or corrected by three methods: (1) increased dietary intake of potassium; this is a pleasant method of supplementing potassium; however, it must be remembered that potassium rich foods are also high in calorie content (9 KCal/mEq of K) (2) potassium chloride supplement; this is an effective method and 24-36 mEq of potassium should be given per day to groups (a) to (e). Patients from group (f) need 100 mEq/day as they lose much of the potassium supplement in the urine. This last group benefits from concurrent administration of a potassium sparing diuretic. Routine administration of supplemental potassium is probably not necessary when diuretics are used to treat hypertension and in young, ambulatory patients with good appetite. (3) Potassium sparing diuretics. They are valuable but when they are given, potassium supplements should be omitted except in cirrhotic patients so that hyperkalemia is avoided. Their use has already been discussed in detail.

(iv) *Hyperkalemia*: This is less common. It occurs in cases with uremia and with drugs like triamterene. It is sometimes seen following massive diuresis with any potent drug; this is probably due to failure of potassium secretion by kidney tubules because of less availability of sodium at potassium secretory sites, after initial marked loss of sodium. The treatment of hyperkalemia is discussed elsewhere.

(v) *Hypochloremic alkalosis*: This occurs following mercurials, thiazides, frusemide and ethacrynic acid. It is caused by excessive loss of chlorides.

(vi) *Metabolic acidosis*: This is seen follow-

ing carbonic anhydrase inhibition (acetazolamide), and is discussed in detail elsewhere.

(vii) *Chronic dilutional hyponatremia*: This state is sometimes seen in patients with congestive cardiac failure where serum sodium is persistently low in spite of severe edema. This is because there is relatively more water retention than sodium retention by the kidneys resulting in extreme dilution of ECF. The mechanisms underlying development of the hyponatremic state are not clear. Although it is not a direct consequence of diuretic therapy, it may be aggravated following most of the diuretics. Such patients usually have severe myocardial impairment and are unresponsive to the diuretics. The prognosis is usually poor, the treatment is difficult and replacement therapy with salt to raise serum sodium level is seldom successful. Rigid restriction of water intake (less than 700-800 ml. daily) is recommended. Glucocorticoids have been claimed to be useful in some of these cases.

When serum sodium concentration approaches the normal value, the patient may exhibit responsiveness to a diuretic.

(c) *Selective adverse effects*: These are discussed under each individual drug and include such toxic effects as renal tubular necrosis following mercurials or hyperglycemia and hyperuricemia following thiazides.

With proper use of diuretic drugs, there would be only a few patients who show refractoriness. In many such cases, correction of underlying electrolyte disturbances restores the responsiveness. In others where GFR is markedly reduced, intravenous administration of aminophylline given at expected peak of action of the primary diuretic drug may produce the desired response. Treatment of extra-renal factors such as pulmonary infection, adequate bed rest and proper use of other drugs like digoxin may help some of the patients. However, in terminal cases of edema, where the underlying pathology is continuously progressing and not correctable, no treatment is likely to prove useful.

ANTIDIURETIC AGENTS

ANTIDIURETIC HORMONE (ADH): The antidiuretic hormone is released from the posterior lobe of the pituitary along with oxytocin. Given in pharmacological doses, it also has a vasopressor action and hence, is also called vasopressin.

The hormone is formed by the supraoptic and paraventricular nuclei of the hypothalamus and travels along the hypothalamohypophyseal tract to the posterior pituitary where it is stored. The rate of secretion of ADH is mainly determined by the state of hydration. Thus, dehydration stimulates whereas hydration inhibits the secretion of the hormone. An increase or a decrease in the circulating blood volume may also influence the secretion through ill-defined 'volume receptors' found in the heart and the pulmonary veins and postulated in the hypothalamus. Usually, ADH and oxytocin are released simultaneously. Drugs like morphine, nicotine and barbiturates can stimulate the release of ADH. Alcohol and chlorpromazine, on the other hand, depress ADH release.

Chemically, ADH is a polypeptide. The amino acid sequence of the hormone varies from animal to animal. Human antidiuretic hormone is 'arginine vasopressin'.

Physiological and pharmacological actions: The predominant actions of ADH are on the kidneys and the cardiovascular system.

I. Kidney: Under the influence of ADH, the distal tubule and the collecting duct of the nephron become permeable to water, leading to a reduction in the total urine volume. The electrolyte pattern of the urine, however, is not altered. Absence of ADH causes diabetes insipidus.

II. Cardiovascular System : In large doses, ADH raises the blood pressure by direct stimulation of the vascular smooth muscle. This rise might be preceded by a transient fall due to narrowing of the coronary vessels. The hormone causes an initial tachycardia, probably secondary to coronary insufficiency and resultant hypoten-

sion, followed by bradycardia. The latter is partly due to rise in blood pressure and partly caused by the direct depressant effect of ADH on the myocardium.

III. Other smooth muscles: When given in large doses, ADH stimulates the smooth muscle of the gastrointestinal tract, promoting peristalsis. The action is greater on the small than on the large intestines. It has very little oxytocic activity.

Absorption, fate and excretion: ADH is inactivated by trypsin in the gastrointestinal tract and has to be administered parenterally for therapeutic effect. When administered subcutaneously or intramuscularly, the drug remains in the body only for a few hours; given intravenously, it is rapidly destroyed. Posterior pituitary powder, used as nasal snuff, has an antidiuretic effect for a period of 6 to 12 hours. However, vasopressin tannate in oil, a repository form administered subcutaneously or intramuscularly, produces an effect lasting for 24 to 48 hours.

ADH is rapidly destroyed in the body largely during passage through the liver and the kidney. Its estimated half life in the plasma is 20 minutes or less.

Adverse reactions: Large doses of vasopressin, administered parenterally, may produce abdominal cramps due to increased peristaltic activity, and backache in women due to stimulation of uterine smooth muscle. Rarely, hypotension and shock may result probably due to coronary spasm, particularly in patients with hypertension or a vascular disease. Nasal irritation and ulceration may occur following repeated nasal insufflation of desiccated posterior pituitary powder.

Bioassay: The antidiuretic activity of vasopressin is bioassayed by its ability to reduce the output of urine in healthy male rats, fasted overnight and hydrated with distilled water in the dose of 5 ml. per 100 g. body weight.

The pressor activity is bioassayed by its pressor effect on blood pressure of a spinal cat or a pithed rat.

A radiomunoassay for vasopressin is now available.

Preparations and dosage :

(i) Vasopressin injection I.P. (Pitressin) is a sterile aqueous solution containing 20 units per ml; dose 0.25 to 0.75 ml. by subcutaneous or intramuscular route. It has a very short duration of action and is therefore not used in treating diabetes insipidus. Its main use is to establish the diagnosis of diabetes insipidus.

(ii) Vasopressin tannate injection N.F. is an oily suspension containing 5 pressor units per ml. Dose 0.5 to 1 ml. once in 24-72 hours. On standing, the drug settles down at the bottom of the ampoules as a yellow residue. The ampoule, therefore, should be warmed gently and shaken vigorously before administration.

(iii) Desiccated posterior pituitary powder, used as snuff by insufflation; dose : 10 to 50 mg. every time the bladder is emptied.

(iv) Synthetic vasopressin analogue, DDAVP (1-deamino-8-D-arginine-vasopressin, Desmopressin), administered intranasally 15 µg. twice daily, is a preparation with greater antidiuretic and decreased pressor activity. It can also be given by injection. Its action is more prolonged, 13-22 hours. It is expensive.

(v) Lysine-8-vasopressin (Syntopressin) is more stable and has activity of 50 units per ml. It is used intranasally by spray.

Therapeutic uses:

(1) **Diabetes insipidus:** Vasopressin tannate is the preparation of choice in this condition. Nasal insufflation is probably the cheapest but has disadvantage of erratic absorption while aqueous preparation has too short a duration of action. Nephrogenic diabetes insipidus does not respond to vasopressin therapy.

(2) **Oesophageal varices and portal hypertension:** Vasopressin, infused intravenously in the dose of 20 units within a period of 30 minutes, produces a marked splanchnic vasoconstriction, reducing thereby the portal flow and

venous pressure. It can also be given by continuous infusion. It may cause fall in cardiac output and coronary artery vasoconstriction. Triglycyl lysine vasopressin (Glypressin), a new analogue, has practically no activity by itself on smooth muscle but *in vivo* it results in a slow release of active hormone. The effect, therefore, lasts for 10 hours after a single bolus injection as compared to the equipotent dose of vasopressin which is active only for 30-40 minutes. It is claimed to control the bleeding better than vasopressin.

BENZOTHIADIAZINES: Surprisingly, benzothiadiazines are effective in controlling pituitary as well as nephrogenic diabetes insipidus. Their mechanism of action in this condition is uncertain and various possibilities have been suggested; they probably act by causing a negative sodium balance and reducing the GFR. This leads to a decrease in volume and an increase in concentration of urine. A long acting drug such as polythiazide is usually preferred. Since symptomless hypokalemia is commonly associated with this therapy, a potassium sparing diuretic may be added to this regimen. In nephrogenic diabetes insipidus, where there is renal unresponsiveness to the action of vasopressin, thiazides are the most effective form of therapy available.

In both idiopathic and nephrogenic diabetes insipidus, the beneficial effect of benzothiadiazines is reduced by liberal salt intake.

CHLORPROPAMIDE: This drug, used in the treatment of diabetes mellitus, has been shown to be effective in the treatment of diabetes insipidus. Interestingly the closely related compounds tolbutamide and glibenclamide are not effective. The exact mechanism of its action is not known. It probably acts by increasing the sensitivity of renal tubules to low and otherwise ineffective concentrations of vasopressin. Unlike thiazide diuretics, the response to chlorpropamide is not reduced by high sodium intake

or steroid administration; further, it is not useful in nephrogenic diabetes insipidus. It is usually given in the dose of 500 mg. daily orally. If hypoglycemia supervenes the dose is reduced to 250 mg. daily (Also see Chapter 60).

Carbamazepine (400-600 mg/day) has been shown to be effective in patients with partial diabetes insipidus. It probably acts by stimulating vasopressin release from the neurohypophysis. Action of carbamazepine and chlorpropamide is overcome by ethanol, which inhibits the release of ADH in man.

DRUGS AND NEPHROTOXICITY

Among the various body organs the kidney is particularly vulnerable to the toxic actions of drugs. This is because it is the major excretory organ for various drugs and their metabolites. Hence, in the presence of renal insufficiency drugs tend to accumulate. Kidney has a rich blood supply and further, it can concentrate the drugs and their polar metabolites locally, thus exposing the renal tubules to very high concentrations of the drugs.

Nephrotoxicity can be 'acute' leading to acute renal failure or may be 'chronic' and responsible for chronic renal disease. Drugs can produce such toxicity by damaging the kidney at many sites from renal arteries to the ureters. Drugs can also cause the renal damage by crystal or calculi formation. From among the many compounds incriminated in producing such renal damage, only some of the better known nephrotoxic agents are included in Table 35.3. These drugs are discussed elsewhere.

Chronic nephropathy due to prolonged ingestion of analgesics has received considerable attention. Patients suffering from this syndrome may present with hematuria, renal colic, urinary infection and finally hypertension and renal failure. The lesions are reversible if the syndrome is detected early and the offending drug stopped. Although at present most of the blame is levelled against phenacetin, contribution by other NSAID in causing this syndrome cannot be totally ruled out. (see Chapter 9)

Drug-induced nephrotic syndrome has been observed following therapeutic use of drugs like tolbutamide, probenecid, troxidone, penicillam-

Table 35.3 : Drugs causing Nephrotoxicity

Site of action	Drugs	Nature of Toxicity
Extra-renal	Tetracyclines, Corticosteroids.	Aggravation of azotaemia probably via increased protein breakdown
Arteries and arterioles	Heavy metals e.g. Arsenic, Bismuth and Gold salts, Horse serum, Long acting sulfonamides, Iodides, Thiazides.	Vasculitis.
Glomeruli	Hydralazine, Long acting sulfonamides.	Vasculitis with glomerulopathy
Convolutated tubules	Aminoglycoside antibiotics, e.g. Kanamycin, Gentamycin, Organic Mercurials, Colistin, Amphotericin B, Polymyxin B, Cephaloridine.	Necrosis of proximal and/or distal tubular epithelium.
Interstitialium	Phenacetin, Phenylbutazone, Sodium diphenyl hydantoin, Sulfonamides	Interstitial nephritis with papillary necrosis. May cause acute renal failure or chronic nephropathy.
Collecting ducts	Acetazolamide, Sulfonamides, Antineoplastic drugs.	Crystalluria, Calculi, Hyperuricaemia.
Ureters	Methysergide.	Obstruction due to retroperitoneal fibrosis.

ine, perchlorate and gold salts. It is characterised by marked proteinuria. Its mechanism is not known. Cessation of the drug usually corrects the abnormality. Certain compounds like anti-epileptic drugs, sulfonamides, tetracyclines, PAS, antihypertensive agents like hydralazine, methyldopa and phenylbutazone can induce systemic lupus erythematosus (SLE) and affect the kidney. The syndrome may be reversible on discontinuation of the offending drug, though this is not always so.

Apart from the therapeutic agents, many poisons also cause nephrotoxicity. These include such compounds as aniline, carbon tetrachloride, phenol, ethylene glycol, phosphorus, arsenic and mercuric chloride.

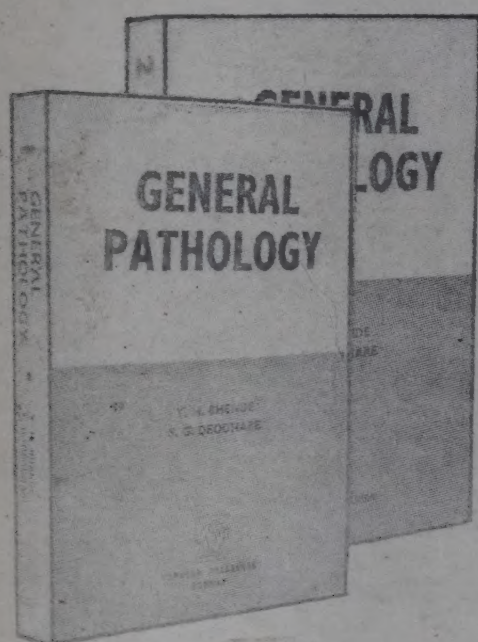
In patients with impaired renal function it is

necessary to reduce the doses of certain drugs to avoid toxicity. This is discussed with individual drugs elsewhere. In general, the serum creatinine is a useful rough guide to the severity of impairment of renal function. In mild failure, with a GFR of 25-50 ml/min. it is 1.8-2.8 mg% (150-249 $\mu\text{mol./l}$); with a GFR between 10-25 ml/min. it is 2.9-7.9 mg% (250-699 $\mu\text{mol./l}$), while in severe renal failure when the GFR is less than 10 ml/min. serum creatinine is 8 mg% (about 700 $\mu\text{mol./l}$) or higher. Renal function deteriorates with age but this reduction, until marked, is not reflected in the serum creatinine level. It should be noted that many apparently healthy elderly subjects also may have a GFR of less than 50 ml/min. and therefore, caution is needed in prescribing certain drugs to them.

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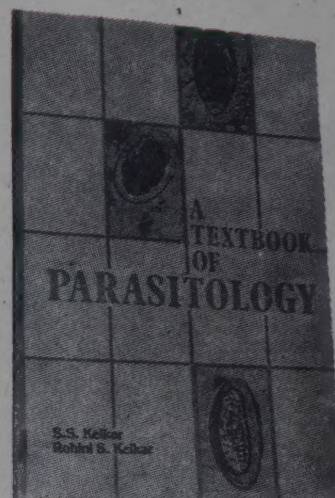
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